United States Department of Agriculture

Folic Acid from Fortified Foods and/or Supplements during Pregnancy and Lactation and Health Outcomes: A Systematic Review

2020 Dietary Guidelines Advisory Committee,
Pregnancy and Lactation Subcommittee

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Nutrition Evidence Systematic Review
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This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee in collaboration with the Nutrition Evidence Systematic Review (NESR) team at the Center for Nutrition Policy and Promotion, Food and Nutrition Service, U.S. Department of Agriculture (USDA). All systematic reviews from the 2020 Advisory Committee Project are available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews.

Conclusion statements drawn as part of this systematic review describe the state of science related to the specific question examined. Conclusion statements do not draw implications, and should not be interpreted as dietary guidance. This portfolio provides the complete documentation for this systematic review. A summary of this review is included in the 2020 Advisory Committee's Scientific Report available at www.DietaryGuidelines.gov.

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USDA and HHS implemented a process to identify topics and scientific questions to be examined by the 2020 Dietary Guidelines Advisory Committee. The Committee conducted its review of evidence in subcommittees for discussion by the full Committee during its public meetings. The role of the Committee members involved establishing all aspects of the protocol, which presented the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria;

[i] Under contract with the Food and Nutrition Service, United States Department of Agriculture.

reviewing all studies that met the criteria they set; deliberating on the body of evidence for each question; and writing and grading the conclusion statements to be included in the scientific report the 2020 Committee submitted to USDA and HHS. The NESR team with assistance from Federal Liaisons and Project Leadership, supported the Committee by facilitating, executing, and documenting the work necessary to ensure the reviews were completed in accordance with NESR methodology. More information about the 2020 Dietary Guidelines Advisory Committee, including the process used to identify topics and questions, can be found at www.DietaryGuidelines.gov. More information about NESR can be found at NESR.usda.gov.

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INTRODUCTION

This document describes a systematic review conducted to answer the following question: What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and health outcomes? This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee, supported by USDA's Nutrition Evidence Systematic Review (NESR).

More information about the 2020 Dietary Guidelines Advisory Committee is available at the following website: www.DietaryGuidelines.gov.

NESR specializes in conducting food- and nutrition-related systematic reviews using a rigorous, protocol-driven methodology. More information about NESR is available at the following website: NESR.usda.gov.

NESR's systematic review methodology involves developing a protocol, searching for and selecting studies, extracting data from and assessing the risk of bias of each included study, synthesizing the evidence, developing conclusion statements, grading the evidence underlying the conclusion statements, and recommending future research. A detailed description of the systematic reviews conducted for the 2020 Dietary Guidelines Advisory Committee, including information about methodology, is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews. In addition, starting on page 135, this document describes the final protocol as it was applied in the systematic review. A description of and rationale for modifications made to the protocol are described in the 2020 Dietary Guidelines Advisory Committee Report, Part D: Chapter 2. Food, Beverage, and Nutrient Consumption During Pregnancy and Chapter 3. Food, Beverage, and Nutrient Consumption During Lactation.

List of abbreviations

Abbreviation	Full name
ADD	Attention deficit disorder
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
BMI	Body mass index
CNPP	Center for Nutrition Policy and Promotion
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
FA	Folic acid
Fe	Iron
FNS	Food and Nutrition Service
HDI	Human Development Index
HHS	Department of Health and Human Services
MCV	Mean corpuscular volume
MTHF	Methyl tetrahydrofolate
MTHFR	Methylenetetrahydrofolate reductase
NESR	Nutrition Evidence Systematic Review
PCS	Prospective cohort study
RASP	Resiliency Attitudes and Skills Profile
RBC	Red blood cell
RCT	Randomized controlled trial
RDW	Red blood cell distribution width
SDQ	Strengths and Difficulties Questionnaire
TEIQue-CSF	Trait Emotional Intelligence Questionnaire Child Short Form
THF	Tetrahydrofolate
USDA	United States Department of Agriculture

WHAT IS THE RELATIONSHIP BETWEEN FOLIC ACID FROM SUPPLEMENTS AND/OR FORTIFIED FOODS CONSUMED BEFORE AND DURING PREGNANCY AND LACTATION AND HEALTH OUTCOMES?

PLAIN LANGUAGE SUMMARY

What is the question?

- What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and micronutrient status?
- What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of gestational diabetes?
- What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of hypertensive disorders during pregnancy?
- What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and human milk composition?
- What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

What is the answer to the question?

Micronutrient status during pregnancy and lactation

Folic acid intake before and during pregnancy:

- Strong evidence indicates that folic acid supplements consumed before and/or during pregnancy are positively associated with folate status (serum, plasma, and/or red blood cell folate).
- Insufficient evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}.
- No evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and red blood cell distribution width.
- No evidence is available to determine the relationship between folic acid from fortified foods consumed before and/or during pregnancy and micronutrient status.

Folic acid intake during lactation:

- Moderate evidence indicates that folic acid supplements consumed during lactation are positively associated with red blood cell folate, and may be positively associated with serum or plasma folate.
- Insufficient evidence is available to determine the relationship between folic acid from supplements consumed during lactation and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}.
- No evidence is available to determine the relationship between folic acid from supplements consumed during lactation and red blood cell distribution width.

- No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and micronutrient status.

Gestational diabetes

- Insufficient evidence is available to determine the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and the risk of gestational diabetes.

Hypertensive disorders of pregnancy

- Limited evidence suggests that folic acid supplements consumed during early pregnancy may have a beneficial effect on reducing the risk of hypertensive disorders during pregnancy among women at high-risk (e.g., history of preeclampsia or prepregnancy BMI ≥25 kg/m^2) compared to no folic acid supplementation.
- Moderate evidence indicates that higher levels of folic acid supplements consumed during pregnancy compared to lower levels (including no folic acid supplementation) does not affect the risk of hypertensive disorders during pregnancy among women at low-risk.
- No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and the risk of hypertensive disorders during pregnancy.

Human milk composition

Folic acid intake before and during pregnancy:

- No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed before and during pregnancy and human milk folate.

Folic acid intake during lactation:

- Moderate evidence indicates that folic acid supplements consumed during lactation does not influence folate levels in human milk.
- No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and human milk folate.

Developmental milestones in children

Folic acid intake before and during pregnancy:

- Insufficient evidence is available to determine the relationship between folic acid supplementation before and/or during pregnancy and cognitive, language, and social-emotional development, and risk of autism spectrum disorder in the child.
- No evidence is available to determine the relationship between folic acid from supplements consumed before and during pregnancy and movement and physical development, academic performance, anxiety, depression, or the risk of attention-deficit disorder or attention-deficit/hyperactivity disorder in the child.
- No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and developmental milestones, including neurobehavioral development, in the child.

Folic acid intake during lactation:

- No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed during lactation and developmental milestones, including neurobehavioral development, in the child.

Why was this question asked?

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.

How was this question answered?

- The 2020 Dietary Guidelines Advisory Committee, Pregnancy and Lactation Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.

What is the population of interest?

- The population of interest for folic acid intake is generally healthy women up to 6 months before pregnancy, during pregnancy, and during lactation.
- This review examines several health outcomes in different populations of interest:
    - Micronutrient status in women during pregnancy and lactation,
    - Gestational diabetes in women during pregnancy,
    - Hypertensive disorders in women during pregnancy,
    - Human milk composition in women during lactation, and
    - Developmental milestones including neurocognitive development in offspring from birth to age 18 years.What evidence was found?

What evidence was found?

Micronutrient status during pregnancy and lactation

- This review includes 14 articles that present evidence about folic acid supplementation before/during pregnancy (9 articles) or during lactation (5 articles). No articles present evidence about folic acid intake from fortified foods. Folic acid is the form of folate in supplements and fortified foods. Folate is found naturally in foods and is also the form that is measured in blood.
- The outcomes are all measures of folate and vitamin B_{12} status. Most of the evidence is about folate status. Consistent evidence indicates that taking folic acid supplements before/during pregnancy or during lactation is associated with higher measures of folate status. The evidence included studies with strong designs (e.g. randomized controlled trials).
- Due to inconsistent results or an insufficient number of studies, a conclusion could not be drawn on the association between folic acid supplementation and hemoglobin, mean corpuscular volume (MCV), or vitamin B_{12}.

Gestational diabetes

- One non-randomized controlled trial (NRCT) was included in this body of evidence.
- Due to an insufficient number of studies, a conclusion could not be drawn on the association between folic acid supplementation before/during pregnancy and risk of

gestational diabetes.

Hypertensive disorders of pregnancy

- Eight articles are included in the evidence about folic acid supplementation before and during pregnancy. No articles present evidence about folic acid intake from fortified foods.
- All articles were about the risk of hypertensive disorders during pregnancy, including high blood pressure, preeclampsia, and eclampsia. The evidence was different for women with a high risk of developing hypertensive disorders (e.g. women who had preeclampsia in a previous pregnancy; women who began pregnancy with over weight or obesity) compared to women with a low risk of developing hypertensive disorders:
    - For women with high risk: A few studies suggest that taking folic acid supplements during early pregnancy may be associated with a lower risk of hypertensive disorders. The evidence is somewhat inconsistent and is limited because it is based on a few studies, including studies with weak study designs.
    - For women with low risk: The evidence suggests that taking more folic acid from supplements compared to taking smaller amounts of folic acid supplements or not taking any folic acid supplements during pregnancy does not affect the risk of hypertensive disorders. The evidence is somewhat consistent and is based on a variety of studies, including studies with a strong study design (e.g. randomized controlled trials).

Human milk composition

- Four articles are included in the evidence about folic acid supplementation during lactation. No articles present evidence about folic acid supplementation before or during pregnancy or about folic acid intake from fortified foods.
- None of the studies found that folic acid supplementation during lactation was associated with folate levels in human milk. The evidence was consistent and included studies with strong designs (e.g. randomized controlled trials).
- All of the studies included women who likely had adequate folate status, so the evidence may be different for women who are folate deficient.

Developmental milestones in children

- This review includes 6 articles that present evidence about folic acid supplementation before/during pregnancy. No articles present evidence about folic acid supplementation during lactation or about folic acid intake from fortified foods.
- The evidence included studies about outcomes in children, such as cognitive development (2 articles), language/communication development (2 articles), social-emotional development (1 article), and autism spectrum disorder (ASD; 1 article). Generally, folic acid supplementation before or during pregnancy was either not associated with or was associated with better had a beneficial association with these outcomes. However, due to inconsistent results or an insufficient number of studies, a conclusion could not be drawn for cognitive

development, language/communication development, social-emotional development, or risk of ASD.

- There was no evidence about whether folic acid supplementation before/during pregnancy was associated with movement/physical development, academic performance, attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD), anxiety, or depression.

How up-to-date is this systematic review?

- This review searched for studies:
  - Micronutrient status: from January 1980 to June 2019
  - Gestational diabetes: from January 1980 to July 2019
  - Hypertensive disorders of pregnancy: from January 1980 to July 2019
  - Human milk composition: from January 1980 to June 2019
  - Developmental milestones: from January 1980 to July 2019

TECHNICAL ABSTRACT

Background

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.
- The 2020 Dietary Guidelines Advisory Committee, Pregnancy and Lactation Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.
- The goal of this systematic review was to examine the following questions:
  - What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and micronutrient status?
  - What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of gestational diabetes?
  - What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of hypertensive disorders during pregnancy?
  - What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and human milk composition?
  - What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

Conclusion statements and grades

- **Micronutrient status**

  Pregnancy

  - Strong evidence indicates that folic acid supplements consumed before and/or during pregnancy are positively associated with folate status (serum, plasma, and/or red blood cell folate). (Grade: Strong)
  - Insufficient evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and red blood cell distribution width. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between folic acid from fortified foods consumed before and/or during pregnancy and micronutrient status. (Grade: Grade not assignable)

  Lactation

  - Moderate evidence indicates that folic acid supplements consumed during lactation are positively associated with red blood cell folate, and may be positively associated with serum or plasma folate. (Grade: Moderate)
  - Insufficient evidence is available to determine the relationship between folic

acid from supplements consumed during lactation and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}. Grade: Grade not assignable
    - No evidence is available to determine the relationship between folic acid from supplements consumed during lactation and red blood cell distribution width. (Grade: Grade not assignable)
    - No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and micronutrient status. (Grade: Grade not assignable)

- **Gestational diabetes**
    - Insufficient evidence is available to determine the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and the risk of gestational diabetes. (Grade: Grade not assignable)

- **Hypertensive disorders of pregnancy**
    - Limited evidence suggests that folic acid supplements consumed during early pregnancy may have a beneficial effect on reducing the risk of hypertensive disorders during pregnancy among women at high-risk (e.g., history of preeclampsia or prepregnancy BMI ≥25 kg/m^2) compared to no folic acid supplementation. (Grade: Limited)
    - Moderate evidence indicates that higher levels of folic acid supplements consumed during pregnancy compared to lower levels (including no folic acid supplementation) does not affect the risk of hypertensive disorders during pregnancy among women at low-risk. (Grade: Moderate)
    - No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and the risk of hypertensive disorders during pregnancy. (Grade: Grade not assignable)

- **Human milk composition**

  Pregnancy
    - No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed before and during pregnancy and human milk folate. (Grade: Grade not assignable)

  Lactation
    - Moderate evidence indicates that folic acid supplements consumed during lactation does not influence folate levels in human milk. (Grade: Moderate)
    - No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and human milk folate. (Grade: Grade not assignable)

- **Developmental milestones**

  Pregnancy

  - Insufficient evidence is available to determine the relationship between folic acid supplementation before and/or during pregnancy and cognitive, language, and social-emotional development, and risk of autism spectrum disorder in the child. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between folic acid from supplements consumed before and during pregnancy and movement and physical development, academic performance, anxiety, depression, or the risk of attention-deficit disorder or attention-deficit/hyperactivity disorder in the child. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and developmental milestones, including neurobehavioral development, in the child. (Grade: Grade not assignable)

  Lactation

  - No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed during lactation and developmental milestones, including neurobehavioral development, in the child. (Grade: Grade not assignable)

Methods

- Three literature searches were conducted using 4 databases (PubMed, Cochrane, Embase, and CINAHL) to identify articles that evaluated:
  - the intervention or exposure of folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and the outcomes of 1) micronutrient status and 2) human milk composition
  - the intervention or exposure of folic acid from supplements and/or fortified foods consumed before and during pregnancy and the outcomes of 1) gestational diabetes and 2) hypertensive disorders during pregnancy
  - the intervention or exposure of folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and the outcomes of developmental milestones, including neurocognitive development, in the child

  A manual search was conducted to identify articles that may not have been included in the electronic databases searched. Articles were screened by two NESR analysts independently for inclusion based on pre-determined criteria
- Data extraction and risk of bias assessment were conducted for each included study, and both were checked for accuracy. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement(s), and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability.

Summary of the evidence

Micronutrient status

Pregnancy

- Nine studies were identified through a literature search from 1980 to 2019 which met the criteria for inclusion in this systematic review. Studies included in this review assessed interventions and exposures before and/or during pregnancy: 6 randomized controlled trials (RCTs), 2 prospective cohort studies (PCSs), and 1 retrospective cohort study.
- Studies varied in intervention details, including:
    - Folic acid supplement type (folic acid or 5-methyl tetrahydrofolate [5-MTHF]).
    - Dose and comparator:
        - Three RCTs and 2 cohort studies compared no folic acid supplementation to folic acid supplementation (RCTs: 350 µg/d to 1.0 mg/d; cohorts: 400 µg/d or dose unknown).
        - Two RCTs compared different levels of folic acid supplementation (330 µg/d vs 730 µg/d; 1.1 mg/d vs 5.0 mg/d).
        - One RCT compared folic acid to 5-MTHF supplementation at the same dose (1.0 mg/d).
    - Duration (2, 3, 5.5, 7, or 12 months).
- Of the 5 outcome measures defined in the analytic framework, all but red blood cell (RBC) distribution width were reported in the body of evidence.
- All but 1 study found a significant association between folic acid supplementation and at least one outcome measure.
- All 9 studies (6 RCTs; 3 PCSs) assessed plasma or serum folate.
    - Of those, 6 found that supplementation was associated with higher values on at least 1 measure of plasma or serum folate and 2 found no association. Another study compared supplementation with folic acid vs 5-MTHF and found that both groups increased over time.
- Six studies (4 RCTs; 2 PCSs) assessed RBC folate.
    - Five found that supplementation was associated with higher values on at least 1 measure of RBC folate and 1 found no association.
- Three studies (2 RCTs; 1 retrospective cohort) assessed hemoglobin. The findings were inconsistent; therefore a conclusion statement could not be drawn.
- Of the 2 RCTs that assessed mean corpuscular volume (MCV), neither found a significant effect on MCV, but study limitations and the small number of studies provided insufficient evidence to draw a conclusion.
- Only 1 RCT assessed the effect of supplementation on vitamin B_{12}; therefore, a conclusion could not be drawn.
- The body of evidence had important limitations:
    - None of the studies preregistered data analysis plans, indicating a risk of bias due to selectivity in results presented.
    - The cohort studies did not adequately account for potential confounding.
    - Risk of bias due to classification of exposures or deviations from intended exposures was a concern for the cohort studies.
    - The study populations did not fully represent the racial/ethnic or

socioeconomic diversity of the U.S. population.
    - No studies met the inclusion criteria that examined the effect of intake of folic acid from fortified foods on the outcome of interest.

Lactation

- Five articles from 4 studies were identified through a literature search from 1980 to 2019, which met the criteria for inclusion in this systematic review. Studies included in this review assessed interventions and exposures during lactation: 3 RCTs, 1 uncontrolled before-and-after study, and 1 PCS that was nested within one of the RCTs.
- Studies varied in intervention details. including:
    - Folic acid supplement type (folic acid or 5-methyltetrahydrofolate [5-MTHF])
    - Dose and comparator
        - Three RCTs and 1 PCS compared no folic acid supplementation to folic acid supplementation (300 µg/d to 1.0 mg/d)
        - One RCT also compared folic acid to 5-MTHF supplementation at the same dose (400 µg/d)
        - One uncontrolled before-and-after study compared folate levels before to after supplementation of 1.0 mg/d synthetic folic acid
    - Duration (1 month, 3 months, 4 months)
- Of the 5 outcome measures defined in the analytic framework, all but RBC distribution width were reported in the body of evidence.
- All studies found a significant association between folic acid supplementation and at least 1 outcome measure.
- All 4 studies assessed plasma or serum folate:
    - Four studies (5 articles: 3 RCTs; 1 PCS; 1 uncontrolled before-and-after study) assessed the relationship between folic acid from supplements during lactation. Two found that supplementation was associated with higher values on at least 1 measure of plasma/serum folate and two found no association.
- All 4 studies assessed RBC folate.
    - All 4 studies (5 articles: 3 RCTs; 1 PCS; 1 uncontrolled before-and-after study) that assessed supplementation during lactation found that supplementation was associated with higher values on at least one measure of RBC folate.
- Two RCTs assessed hemoglobin. The findings were inconsistent and therefore a conclusion statement could not be drawn.
- One RCT each assessed the effect of supplementation on MCV or vitamin B_{12} status; therefore, conclusions could not be drawn.
- This body of evidence had important limitations:
    - None of the studies preregistered data analysis plans, indicating a potential risk of bias due to selectivity in results presented.
    - Neither the PCS nor the uncontrolled before-and-after study adequately accounted for potential confounding.
    - Risk of bias due to classification of exposures or deviations from intended exposures was a concern for the cohort study and the uncontrolled before-and-after study.

    - The study populations did not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.
    - No studies that examined the effect of intake of folic acid from fortified foods on the outcome of interest met the inclusion criteria.

Gestational diabetes

- One non-RCT (NRCT) that met the criteria for inclusion in this systematic review was identified through a literature search from 1980 to 2019.
- This study found that women who consumed folic acid supplementation based on genotype and stage of pregnancy had significantly fewer cases of gestational diabetes compared to women who did not consume folic acid supplements before or during pregnancy.
- The evidence had several limitations:
    - No baseline data on study groups were provided for comparison.
    - Intervention methods and adherence were not clear.
    - Results by subgroup were not reported.
    - Consistency could not be assessed with only 1 study.

Hypertensive disorders of pregnancy

- Eight studies, including 3 RCTs, 2 NRCTs, and 3 PCSs, met the criteria for inclusion in this systematic review, which were identified through a literature search from 1980 to 2019.
- The 3 RCTs compared 5.0 mg/d of folic acid supplementation to a lower-dose of either 0.5 mg/d (2 studies) or 1.0 mg/d (1 study) from early pregnancy through delivery. The folic acid supplementation dose had no effect on incidence of gestational hypertension, preeclampsia, or eclampsia. None of the studies compared folic acid supplementation to a control group with no folic acid supplementation.
- The 2 NRCTs found a statistically significant association of folic acid supplementation (15 mg/d of 5-MTHF in one study; 400-800 µg/d in another study) from early pregnancy through delivery on risk of gestational hypertension or preeclampsia compared to a control group with no folic acid supplementation. One NRCT was among a high-risk population (women who had preeclampsia in their preceding pregnancy); the other had methodological limitations related to exposure, outcome assessment, and analysis.
- The 3 PCSs reported mixed results. One study found an association between folic acid use in the first trimester and lower incidence of preeclampsia in the full study sample, and specifically among those with a BMI ≥25 kg/m^2; another study found a statistically significant association between folic acid use at 12 to 20 weeks gestation and lower incidence of preeclampsia among high-risk women. A third study did not find a significant association between folic acid supplementation pre and/or post-conception (Four weeks before to 8 weeks after last menstrual period) and preeclampsia. In addition to problems related to confounding, these studies did not account for potential changes in folic acid supplementation during pregnancy.
- No articles were identified that met the inclusion criteria related to folic acid intake from fortified foods and risk of hypertensive disorders during pregnancy.

Human milk composition

Pregnancy

- No studies related to folic acid intake from supplements during pregnancy which met the criteria for inclusion in this systematic review were identified through a literature search from 1980 to 2019.

Lactation

- Four studies were identified through a literature search from 1980 to 2019, which met the criteria for inclusion in this systematic review: 3 RCTs and 1 uncontrolled before-and-after study.
- Studies varied in intervention details, including folic acid supplement type (folic acid, 5-methyltetrahydrofolate, or pteroylmonoglutamate), dose (300 µg/d, 400 µg/d, or 1 mg/d), time of initiation (1 to 25 weeks postpartum), duration (4 weeks, 12 weeks, or 16 weeks), and sample characteristics.
- As defined by the inclusion criteria, all studies took place in high or very high Human Development Index countries; therefore, the participants were likely to be folate replete.
- None of the studies found an association between folic acid supplementation in women who were lactating and milk folate levels.
- This body of evidence had important limitations:
    - In one of the 3 RCTs, the reference group was not recruited and randomized with the other 2 study groups. In another study, milk folate was significantly different between the control and intervention groups at baseline, and this was not controlled for in the analyses.
    - Only 1 study reported a power calculation and that study did not reach the target sample size.
    - The study populations did not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.

Neurocognitive development of the child

Pregnancy

- Six articles that met the criteria for inclusion in this systematic review were identified through a literature search from 1980 to 2019. The articles report findings from 4 studies representing 4 outcome domains:
    - Cognitive development: 1 RCT; 2 articles.
    - Language and communication development: 1 PCS; 2 articles.
    - Social-emotional development: 1 RCT; 1 article.
    - ASD: 1 nested case-control study; 1 article.
- Generally, folic acid supplementation before or during pregnancy was either not associated with or had a beneficial association with the included outcomes.
- For cognitive development, findings were inconsistent; therefore a conclusion statement could not be drawn.
- For social-emotional development, only 1 study was available and it had some limitations; therefore, a conclusion could not be drawn.
- For language development, 2 articles were included from the Norwegian Mother and Child (MoBa) cohort. These articles reported a lower risk of severe language delay in children age 3 years whose mothers had taken folic acid supplements during early pregnancy compared to children whose mothers either did not take folic acid

during pregnancy or took folic acid supplements later in pregnancy.

- For ASD, 1 nested case-control found a significant association between folic acid supplementation before pregnancy and during pregnancy and lower risk of ASD in children ages 8 to 12 years, compared to no folic acid supplementation. This was true for a number of subgroups within the sample, including children without siblings, males, females, children with low socioeconomic status, children with both parents with psychiatric diagnosis, and children without intellectual disabilities.
- No evidence was found on whether folic acid supplementation before and/or during pregnancy was associated with other included outcomes: movement and physical development, academic performance, ADD or ADHD, anxiety, or depression.
- No evidence was found on folic acid from supplements or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development.

Lactation

- The search identified 0 studies published between 1980 and 2019 that met the inclusion criteria.

FULL REVIEW

Systematic review question—Micronutrient status

What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and micronutrient status?

Conclusion statements and grades

Pregnancy

- Strong evidence indicates that folic acid supplements consumed before and/or during pregnancy are positively associated with folate status (serum, plasma, and/or red blood cell folate). (Grade: Strong)
- Insufficient evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}. (Grade: Grade not assignable)
- No evidence is available to determine the relationship between folic acid from supplements consumed before and/or during pregnancy and red blood cell distribution width. (Grade: Grade not assignable)
- No evidence is available to determine the relationship between folic acid from fortified foods consumed before and/or during pregnancy and micronutrient status. (Grade: Grade not assignable)

Lactation

- Moderate evidence indicates that folic acid supplements consumed during lactation are positively associated with red blood cell folate, and may be positively associated with serum or plasma folate. (Grade: Moderate)
- Insufficient evidence is available to determine the relationship between folic acid from supplements consumed during lactation and hemoglobin, mean corpuscular volume, and serum vitamin B_{12}. (Grade: Grade not assignable)
- No evidence is available to determine the relationship between folic acid from supplements consumed during lactation and red blood cell distribution width. (Grade: Grade not assignable)
- No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and micronutrient status. (Grade: Grade not assignable)

Summary of the evidence

Pregnancy

- Nine studies were identified through a literature search from 1980 to 2019 which met the criteria for inclusion in this systematic review.[1-9] Studies included in this review assessed interventions and exposures before and/or during pregnancy: 6 randomized controlled trials (RCTs), 2 prospective cohort studies (PCSs), and 1 retrospective cohort study.
- Studies varied in intervention details, including:
    - Folic acid supplement type (folic acid or 5-methyl tetrahydrofolate [5-MTHF]).
    - Dose and comparator:

        - Three RCTs and 2 cohort studies compared no folic acid supplementation to folic acid supplementation (RCTs: 350 µg/d to 1.0 mg/d; cohorts: 400 µg/d or dose unknown).
        - Two RCTs compared different levels of folic acid supplementation (330 µg/d vs 730 µg/d; 1.1 mg/d vs 5.0 mg/d).
        - One RCT compared folic acid to 5-MTHF supplementation at the same dose (1.0 mg/d).
    - Duration (2, 3, 5.5, 7, or 12 months).
- Of the 5 outcome measures defined in the analytic framework, all but red blood cell (RBC) distribution width were reported in the body of evidence.
- All but 1 study found a significant association between folic acid supplementation and at least one outcome measure.
- All 9 studies (6 RCTs; 3 PCSs) assessed plasma or serum folate.
    - Of those, 6 found that supplementation was associated with higher values on at least 1 measure of plasma or serum folate and 2 found no association. Another study compared supplementation with folic acid vs 5-MTHF and found that both groups increased over time.
- Six studies (4 RCTs; 2 PCSs) assessed RBC folate.
    - Five found that supplementation was associated with higher values on at least 1 measure of RBC folate and 1 found no association.
- Three studies (2 RCTs; 1 retrospective cohort) assessed hemoglobin. The findings were inconsistent; therefore a conclusion statement could not be drawn.
- Of the 2 RCTs that assessed mean corpuscular volume (MCV), neither found a significant effect on MCV, but study limitations and the small number of studies provided insufficient evidence to draw a conclusion.
- Only 1 RCT assessed the effect of supplementation on vitamin B_{12}; therefore, a conclusion could not be drawn.
- The body of evidence had important limitations:
    - None of the studies preregistered data analysis plans, indicating a risk of bias due to selectivity in results presented.
    - The cohort studies did not adequately account for potential confounding.
    - Risk of bias due to classification of exposures or deviations from intended exposures was a concern for the cohort studies.
    - The study populations did not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.
    - No studies met the inclusion criteria that examined the effect of intake of folic acid from fortified foods on the outcome of interest.

Lactation

- Five articles from 4 studies were identified through a literature search from 1980 to 2019 which met the criteria for inclusion in this systematic review.[10-14] Studies included in this review assessed interventions and exposures during lactation: 3 RCTs, 1 uncontrolled before-and-after study, and 1 PCS that was nested within one of the RCTs.
- Studies varied in intervention details including:
    - Folic acid supplement type (folic acid or 5-methyltetrahydrofolate [5-MTHF])
    - Dose and comparator

        - Three RCTs and 1 PCS compared no folic acid supplementation to folic acid supplementation (300 µg/d to 1.0 mg/d)
        - One RCT also compared folic acid to 5-MTHF supplementation at the same dose (400 µg/d)
        - One uncontrolled before-and-after study compared folate levels before to after supplementation of 1.0 mg/d synthetic folic acid
    - Duration (1 month, 3 months, 4 months)
- Of the 5 outcome measures defined in the analytic framework, all but RBC distribution width were reported in the body of evidence.
- All studies found a significant association between folic acid supplementation and at least 1 outcome measure.
- All 4 studies assessed plasma or serum folate:
    - Four studies (5 articles: 3 RCTs; 1 PCS; 1 uncontrolled before-and-after study) assessed the relationship between folic acid from supplements during lactation. Two found that supplementation was associated with higher values on at least 1 measure of plasma/serum folate and two found no association.
- All 4 studies assessed RBC folate.
    - All 4 studies (5 articles: 3 RCTs; 1 PCS; 1 uncontrolled before-and-after study) that assessed supplementation during lactation found that supplementation was associated with higher values on at least one measure of RBC folate.
- Two RCTs assessed hemoglobin. The findings were inconsistent and therefore a conclusion statement could not be drawn.
- One RCT each assessed the effect of supplementation on MCV or vitamin B_{12} status; therefore, conclusions could not be drawn.
- This body of evidence had important limitations:
    - None of the studies preregistered data analysis plans, indicating a potential risk of bias due to selectivity in results presented.
    - Neither the PCS nor the uncontrolled before-and-after study adequately accounted for potential confounding.
    - Risk of bias due to classification of exposures or deviations from intended exposures was a concern for the cohort study and the uncontrolled before-and-after study.
    - The study populations did not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.
    - No studies that examined the effect of intake of folic acid from fortified foods on the outcome of interest met the inclusion criteria.

Description of the evidence

This systematic review included articles that address the relationship between folic acid from supplements and/or fortified foods[ii] consumed before and during pregnancy and lactation and micronutrient status. The search included articles from countries categorized as high or very high on the Human Development Index (HDI)[iii] and were published between January 1980 and June 2019. Studies included generally healthy women up to 6 months before pregnancy, during pregnancy, or during lactation at the time of the intervention or exposure. Study designs included were: RCTs, non-randomized controlled trials (NRCT), prospective and retrospective cohort studies, nested case-control studies, and uncontrolled before-and-after.

Thirteen studies (fourteen articles) were included in the body of evidence (see **Figure 6**).[1-14] Basic characteristics of the studies are shown in **Table 1, Table 2,** and **Table 3**. Nine studies were RCTs,[1-6,10-12] and the remaining studies included 3 PCSs,[7,8,13] 1 retrospective cohort study,[9] and 1 uncontrolled before-and-after study.[14]

According to the inclusion criteria, all studies enrolled women from countries with a high or very high HDI rating, including 3 studies (4 articles) from Canada,[6,10,11,13] 2 from the United States,[2,12] and 1 study each from France,[1] Germany,[8] Iran,[3] Ireland,[7] Japan,[14] Mexico,[4] Turkey,[9] and the United Kingdom.[5]

The included studies examined the effect of folic acid supplementation before and/or during pregnancy or lactation on folate status, while no studies examined the effect of folic acid from fortified foods on the outcome of interest. The sample size in these 13 studies ranged from 12 to 397, with group samples ranging from 16 to 294. The study populations do not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.

Participant characteristics

There was some variation in participant characteristics. While nearly all of the studies included women with mean ages of 26 to 34 years, one study included women aged 18 to 35 years[2] and another was conducted in a population of adolescent girls with a mean age of 17 years.[11] Of the four studies that reported data on race or

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[ii] *Dietary supplement* was defined as a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement (ODS; Dietary Supplement Health and Education Act, 1994). *Fortification* was defined as the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food (FDA).

[iii] The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world- country-and-lending-groups).

ethnicity,[5,6,11,12] nearly all participants were identified as White. In 3 studies (4 articles), participants had college degrees and/or were from relatively high socioeconomic backgrounds.[6,10,12,13] Another two studies recruited women from primarily middle or lower socioeconomic backgrounds.[1,11] The study in Japan reported that participants were all from the same socioeconomic group, but did not provide additional details.[14] The remaining studies did not provide information on socioeconomic status.

Interventions/Exposures

Dose and composition

- The form of folic acid supplement varied across studies, and included: folic acid,[2,3,5-9,11,12,14] 5-methyltetrathydrofolate (5-MTHF),[3,10,13] and folinic acid.[4] Ten studies compared some level of folic acid supplementation to no folic acid. This included 4 RCTs that compared either 300 µg/d, 400 µg/d, or 1.0 mg/d folic acid to a placebo[5,10-12]; 2 RCTs that compared an iron supplement with and without folic acid (350 µg/d[1] or 370 µg/d[4]); 1 uncontrolled before-and-after study that compared folate levels before taking folic acid to 4 weeks after taking 1 mg/d folic acid; and 3 cohort studies that compared women who took folic acid supplements to women who did not.[7-9]
- Two studies compared a higher dose with a lower dose of folic acid: Shere et al[6] compared 1.1 mg/d to 5.0 mg/d folic acid, and Caudill et al[2] compared 330 µg/d to 730 µg/d folic acid.
- Two studies (3 articles) included a study arm with 5-MTHF in addition to an arm with folic acid.[3,10,13]
- No studies met the inclusion criteria related to folic acid intake from fortified foods on micronutrient status.

Timing of exposure

- Before and/or during pregnancy: Nine of the included studies initiated supplementation before or during pregnancy. Of these, three studies began supplementation before conception; 2 lasted for 12 months[3,6] and the duration was not clear in 1 study.[9] Two studies examined exposure to folate supplementation in each trimester.[7,8] Three studies initiated supplementation during the second trimester (after gestational week 13) and lasted for either 60 days,[4] 12 weeks,[2] or 22 weeks,[5] although in one study all women,[4] and in another study most women, took a folic acid supplement during the first trimester of pregnancy. Another study began supplementation at gestational week 28 and lasted until delivery.[1]
- During lactation: Of the 4 studies that examined postnatal folate supplementation, 2 initiated supplementation 1 week postpartum, and lasted either 12 weeks[11] or 16 weeks.[10,13] One initiated supplementation at 3 months postpartum and had a 12-week duration.[12] In the uncontrolled before-and-after study, timing of initiation ranged from 3 to 25 weeks postpartum and intervention lasted 4 weeks.[14]

Outcome

Of the predetermined outcome measures for micronutrient status (see **Figure 1**), all except red blood cell distribution width were reported in this evidence base to varying degrees (**Table 1**). All 13 studies examined serum or plasma folate. Of those, 9 studies (6 RCTs,[1-6] 2 PCSs,[7,8] and 1 retrospective cohort study[9]) examined exposure

before and/or during pregnancy, and 4 studies (5 articles: 3 RCTs,[10-12] 1 prospective cohort study,[13] and 1 uncontrolled before-and-after[14]) examined exposure during lactation.

Ten studies assessed RBC folate, including 6 studies (4 RCTs[1,2,5,6]; 2 PCSs[7,8]) that examined supplementation before and/or during pregnancy. Four studies (5 articles: 3 RCTs,[10-12] 1 prospective cohort study,[13] and 1 uncontrolled before-and-after[14]) assessed supplementation during lactation.

Five studies assessed hemoglobin, including 3 studies (2 RCTs[1,4]; 1 retrospective cohort[9]) that examined supplementation before and/or during pregnancy and 2 RCTs[11,12] that assessed the effect of supplementation during lactation.

Of the 3 RCTs that assessed MCV, 2 assessed the effect of supplementation before and/or during pregnancy[1,4] and 1 during lacation.[12]

Two RCTs assessed the effect of supplementation on vitamin B_{12} status during pregnancy[5] or lactation.[11]

Two studies reported folate deficiency, defined as either RBC folate <320 nmol/L[8] or serum folate <4.5 ng/mL,[9] and 1 study reported serum tetrahydrofolate (THF), 5-MTHF, 5-formyl-THF, and unmetabolized folic acid.[10,13]

Table 1. Overview of study characteristics and outcomes assessed[iv,v]

	Intervention/ exposure			Outcomes						
Study	**Timing**	**Design**	**Comparisons**	**Serum/Plasma Folate**	**RBC Folate**	**Hb**	**MCV**	**B_{12}**	**Folate Deficiency**	**Other**
Blot, 1981[1]	Before and/or during Pregnancy	RCT	105 mg/d Fe vs 105 mg/d Fe+ 350 mg/d FA	X	X	X	X	.	.	.
Caudill, 1997[2]	Before and/or during Pregnancy	RCT	330 µg/d FA vs 730 µg/d FA	X	X	.	.	.	.	.
Hekmatdoost, 2015[3]	Before and/or during Pregnancy	RCT	1.0 mg/d 5-MTHF vs 1.0 mg/d FA	X	.	.	.	.	.	.
Juarez-Vazquez, 2002[4]	Before and/or during Pregnancy	RCT	80 mg/d Fe vs 80 mg Fe+0.370 mg Folinic Acid	X	.	X	X	.	.	.
McNulty, 2013[5]	Before and/or during Pregnancy	RCT	0 µg/d Placebo vs 400 µg/d FA	X	X	.	.	X	.	.
Shere, 2015[6]	Before and/or during Pregnancy	RCT	1.1 mg/d FA vs 5.0 mg/d FA	X	X	.	.	.	.	.
Holmes, 2005[7]	Before and/or during Pregnancy	PCS	No FA vs FA (dose NR)	X	X	.	.	.	.	.
Koebnick, 2001[8]	Before and/or during Pregnancy	PCS	Continuous modelling	X	X	.	.	.	X	.
Ozer, 2016[9]	Before and/or during Pregnancy	RCS	No FA vs FA (400 µg/d)	X	.	X	.	.	X	.
Houghton, 2006[10] (2007[13])	Lactation	RCT (PCS)	0 µg/d Placebo vs 400 µg/d FA vs 400 µg/d 5-MTHF	X	X	.	.	.	.	X
Keizer, 1995[11]	Lactation	RCT	0 µg/d Placebo vs 300 µg/d FA	X	X	X	.	X	.	.
Mackey, 1999[12]	Lactation	RCT	0 mg/d Placebo vs 1 mg/d FA	X	X	X	X	.	.	.

[iv] FA: folic acid; Fe: iron; Hb: hemoglobin; MCV: mean corpuscular volume; MTHF: methyltetrahydrofolate; NR: not reported; PCS: prospective cohort study; RBC: red blood cell; RCS: retrospective cohort study; RCT: randomized controlled trial; Unc BA: uncontrolled before-and-after study; X: outcome was reported

[v] "Other" includes: THF, 5-MTHF, 5-formylTHF, unmetabolized folic acid

	Intervention/ exposure			Outcomes						
Tamura, 1980[14]	Lactation	Unc BA	1 mg/d FA: before vs after	X	X	.	.	.	.	.
Total (of 13)				13	10	5	3	2	2	1

Evidence synthesis

Fourteen articles from 13 studies examining the relationship between folic acid intake before and during pregnancy and lactation on folate status were included in this review. All of the studies reported at least one statistically significant finding, thus publication bias is a potential concern with this body of evidence.

Folate status (plasma, serum, and RBC folate): Supplementation before and/or during pregnancy

Summary

Nine studies assessed folate status, as measured by plasma, serum, and/or RBC folate.[1-9] Despite a variety in supplement dose, composition, and comparator group, all but one study found at least one measure of folate status was statistically significantly related to folic acid supplementation before and/or during pregnancy.[9]

Nine studies reported results for plasma folate[3,4,6-8] or serum folate[1-3,5,9] biomarkers that reflects recent folate intake (**Table 1**). These include 6 RCTs,[1-6] 2 prospective cohort studies,[7,8] and 1 retrospective cohort study.[9] The majority of studies (6 of 9) reported higher serum folate[1,2,5] or plasma folate[3,7,8] after folic acid supplementation compared to no supplementation or a lower dose of supplementation (**Table 3**). Three studies found no statistically significant association between folic acid supplementation and serum folate[3,9] or plasma folate.[4] Additionally, one RCT measured the change in plasma folate over time with supplementation of 1.1 mg/d or 5.0 mg/d folic acid during pregnancy.[6] Plasma folate increased from baseline to 6 weeks gestation in both experimental groups followed by a decrease from 6 to 12 weeks gestation, with a faster rate of decline in the 5.0 mg/d group compared to the 1.1 mg/d group. Hekmatdoost et al[3] compared the same dose of 2 forms of folic acid supplementation (1.0 mg/d 5-MTHF and 1.0 mg/d folic acid) from preconception to 20 weeks gestation on plasma folate. That study reported an increase in plasma folate over time in both groups, but the increase was greater in the 5-MTHF group.

Six studies examined the relationship between folic acid supplementation and RBC folate levels, a biomarker of long-term folate status.[1,2,5-8] Five of these reported a significant increase in RBC folate with supplementation of either folic acid or 5-MTHF, while one study found no statistically significant relationship.[2]

Two cohort studies reported prevalence of folate deficiency, defined as either RBC folate <320 nmol/L[8] or serum folate <4.5 ng/mL,[9] as an outcome and found no statistically significant association between folic acid supplementation and prevalence of folate deficiency.

***Assessment of the evidence*[vi]**

The conclusion statement "evidence suggests that folic acid supplements consumed before and/or during pregnancy is positively associated with folate status (serum, plasma, and/or RBC folate)" was assigned a grade of **strong**. This conclusion statement is supported by 6 RCTs and 2 prospective cohort studies, and 1 retrospective cohort study. As outlined and described below, the body of evidence examining folic acid supplementation before and/or during pregnancy and folate status was assessed for the following elements used when grading the strength of evidence:

- **Risk of Bias** was considered strong (i.e., low risk) because the 6 RCTs had few concerns regarding risk of bias (**Table 4**). None of the included studies reported a pre-registered data analysis plan, suggesting a potential risk of bias due to selection of reported results. There was some concern about risk of bias regarding randomization for 2 of the 6 RCTs. Shere et al[6] reported imbalanced plasma folate at baseline between treatment groups and neither participants nor study staff were blinded post-randomization. The study by Caudill et al [2] did not report methods of randomization and provided little information on participant characteristics. For the cohort studies, the risk of bias was considered limited because there were many serious risks of bias (e.g. none of the 3 studies accounted for all key confounders, and all 3 had risk of bias due to classification of exposures because follow-up time from start of supplementation may have differed among women). Participants in the cohort studies may have begun taking folic acid supplements before study enrollment and may have changed exposure status prior to follow up. However, the results of the cohort studies mostly aligned with those of the RCTs, and strength of study design, along with the number of RCTs led to an overall grade of strong for risk of bias (**Table 6**).
- **Consistency** was assigned a grade of strong because 5 of the 6 RCTs showed a positive association between supplementation and folate status, although Hekmatdoost[3] did not have a true control group, because all women received similar quantities of folic acid in one of two forms. One RCT did not find a significant association[4]; however this inconsistency could be explained by the differences in population characteristics compared to the other RCTs (i.e., in the Juarez-Vazquez study,[4] all women had iron deficiency anemia at recruitment), and the study was potentially underpowered to evaluate the relationship between supplementation and folate status. The cohort studies were assigned a grade of moderate for consistency, but were generally consistent with the results of the RCTs.
- **Directness** was considered strong as the studies were designed to assess the exposure, comparator, outcomes, and population as outlined in the Analytic Framework (**Figure 1**).
- **Precision**: Precision was strong for the 6 RCTs. Three of the 6 showed a statistically significant positive association between supplementation and folate status, as assessed by both serum/plasma folate and RBC folate. Two RCTs additionally found a mix of statistically significant and non-significant results across

[vi] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

multiple biomarkers, which could be explained by small sample size[2] or lack of a true control group.[3] One RCT found no statistically significant association with serum folate, which could be due to sample characteristics.[4] Two RCTs did not report power calculations or sample size estimates,[1,2] and 2 reported insufficient analytic sample sizes according power analyses.[4,6] Precision was graded as moderate for the 3 cohort studies.

- **Generalizability**: The RCTs were graded as moderate for generalizability because only 1 of the 6 was conducted in the United States, and had limited racial/ethnicity and socioeconomic diversity. The cohort studies were considered limited because none of the 3 studies reported information on either race/ethnicity or socioeconomic status.

Folate status (plasma, serum, and RBC folate): Supplementation during lactation

Summary

Four studies (5 articles) reported results for plasma folate,[10-14] including 3 RCTs,[10-12], 1 prospective cohort study,[13] and 1 uncontrolled before-and-after study[14] (**Table 1**). No studies reported results for serum folate. Two studies reported higher plasma folate after folic acid supplementation compared to no supplementation (**Table 3**).[10,13,14] Two studies found no statistically significant association between folic acid supplementation and plasma folate.[11,12]

The same four studies examined the relationship between folic acid supplementation and RBC folate levels, and all reported a significant increase in RBC folate with supplementation of either folic acid or 5-MTHF.[10-14]

One RCT measured additional folate biomarkers and found significantly higher levels of plasma 5-formyl-THF after 16 weeks of folic acid supplementation in lactating women compared to women taking a placebo.[10] There were no significant effects on THF, 5-MTHF, or unmetabolized folic acid in serum between the groups.

Assessment of the evidence[vii]

The conclusion statement "evidence suggests that folic acid supplements consumed during lactation is positively associated with RBC folate, and may be positively associated with serum/plasma folate" was graded as **moderate**. This conclusion statement is supported by 3 RCTs and 1 prospective cohort study, and 1 uncontrolled before-and-after study. As outlined and described below, the body of evidence examining folic acid supplementation during lactation and RBC folate was assessed for the following elements used when grading the strength of evidence:

- **Risk of Bias** was moderate for the 3 RCTs. None of the included studies reported a pre-registered data analysis plan, resulting in risk of bias due to selection of

[vii] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

reported results. There was some concern about risk of bias regarding randomization because Houghton et al[10,13] included a group of women taking folic acid supplements who were not randomized, and there were differences in plasma and RBC folate at baseline between treatment groups. The cohort and uncontrolled before-and-after studies were considered limited because both had serious risk of confounding (**Table 4, Table 5, and Table 6**). Further, the study by Tamura et al[14] did not include a control group, reported very little information on participant characteristics and no information on statistical analyses conducted.

- **Consistency** was strong for the RCTs, but a grade could not be assigned for the cohort or uncontrolled before-and-after studies.
- **Directness** was considered strong as the studies were designed to assess the exposure, comparator, outcomes, and population as outlined in the Analytic Framework (**Figure 1**).
- **Precision** was moderate for the RCTs, but a grade could not be assigned for the cohort or uncontrolled before-and-after studies.
- **Generalizability** was considered moderate for RCTs and limited for the cohort and uncontrolled before-and-after studies because only 1 study was conducted in the United States; most participants were from relatively high socioeconomic backgrounds, with little racial/ethnic diversity reported.

Hemoglobin: Supplementation before and/or during pregnancy

Summary

Three studies assessed hemoglobin levels after folic acid supplementation before and/or during pregnancy, including 2 RCTs[1,4] and 1 retrospective cohort study[9] (**Table 1 and Table 3**). One study found higher levels of hemoglobin in women after folic acid supplementation compared to women who did not take folic acid supplements.[4] All women in that study were iron-deficient anemic at baseline. The remaining 2 found no statistically significant association between folic acid supplementation and hemoglobin levels.[1,9]

Assessment of the evidence

The small number of studies produced mixed results, with a lack of consistency in baseline iron status and treatment between studies. There were some concerns regarding risk of bias due to selection of reported results in the RCTs[1,4] because neither study had preregistered data analysis plans (**Table 4**), and risk of bias due to confounding and classification of exposures in the retrospective cohort study[9] (**Table 6**). Therefore, there was insufficient evidence to determine the relationship between folic acid supplementation before and/or during pregnancy and hemoglobin levels, and the body of evidence was rated ‘grade not assignable.’

Hemoglobin: Supplementation during lactation

Summary

Two RCTs assessed hemoglobin levels after folic acid supplementation during lactation (**Table 1 and Table 3**).[11,12] Mackey et al[12] found higher levels of hemoglobin in women after folic acid supplementation compared to women who did not take folic

acid supplements, and Keizer et al[11] found no statistically significant association between folic acid supplementation and hemoglobin levels. Differences in the intervention, including dose and timing of the intervention between Mackey et al (1 mg/d from 3 to 6 months postpartum) and Keizer et al (300 µg/d from 1 to 12 weeks postpartum) did not clearly explain differences in the results.

Assessment of the evidence

The small number of studies produced mixed results, which were not clearly explained by the study methods. There were some concerns regarding one study, which did not report a power calculation or sample size estimate. Both studies had risk of bias due to selection of reported results because neither study had preregistered data analysis plans and risk of bias due to missing outcome data (**Table 4**).[12] Therefore, there was insufficient evidence to determine the relationship between folic acid supplementation during lactation and hemoglobin levels, and the body of evidence was rated 'grade not assignable.'

Mean corpuscular volume: Supplementation before and/or during pregnancy

Summary

Two RCTs assessed the relationship between folic acid supplementation during pregnancy and mean corpuscular volume (MCV), and neither found a significant association (**Table 1 and Table 3**).[1,4] Notably, both studies provided iron supplements to all participants, and 1 study enrolled only women with iron deficiency anemia (**Table 2**).[4]

Assessment of the evidence

Due to the small number of studies, concerns regarding substantial attrition (**Table 2**), and risk of bias due to selection in reporting bias because no studies pre-registered data analysis plans (**Table 4**), there was insufficient evidence to determine the relationship between folic acid supplementation before and/or during pregnancy and MCV. Therefore, the body of evidence was rated 'grade not assignable.'

Mean corpuscular volume: Supplementation during lactation

Summary

One RCT assessed MCV levels after folic acid supplementation during lactation, and found no statistically significant association (**Table 1 and Table 3**).[12]

Assessment of the evidence

The body of evidence was composed of a single study, which had concerns regarding risk of bias due to selection of reported results because there was no pre-registered data analysis plan (**Table 4**). Therefore, there was insufficient evidence to determine the relationship between folic acid supplementation during lactation and MCV, and a grade was not assignable.

Vitamin B_{12}: Supplementation before and/or during pregnancy

Summary

One RCT assessed serum vitamin B_{12} after folic acid supplementation during pregnancy, and found no statistically significant association (**Table 1 and Table 3**).[5]

Assessment of the evidence

The body of evidence was composed of a single study, which had concerns regarding risk of bias due to selection of reported results because there was no pre-registered data analysis plan (**Table 4**). Therefore, there was insufficient evidence to determine the relationship between folic acid supplementation before and/or during pregnancy and vitamin B_{12} levels, and a grade was not assignable.

Vitamin B_{12}: Supplementation during lactation

Summary

One RCT assessed plasma vitamin B_{12} after folic acid supplementation during lactation, and found no statistically significant association (**Table 1 and Table 3**).[11]

Assessment of the evidence

The body of evidence was composed of a single study, which had concerns regarding risk of bias due to selection of reported results because there was no pre-registered data analysis plan and due to missing outcome data (**Table 4**). Therefore, there was insufficient evidence to determine the relationship between folic acid supplementation during lactation and vitamin B_{12} levels, and a grade was not assignable.

Red blood cell distribution width: Supplementation before and/or during pregnancy

Summary

No studies meeting the inclusion criteria for this review examined the relationship between folic acid supplementation before and/or during pregnancy and red blood cell distribution width, and therefore a grade was not assignable.

Red blood cell distribution width: Supplementation during lactation

Summary

No studies meeting the inclusion criteria for this review examined the relationship between folic acid supplementation during lactation and red blood cell distribution width, and therefore a grade was not assignable.

Table 2. Description of studies examining the relationship between consumption of folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and micronutrient status[viii, ix]

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Exposure Before and/or During Pregnancy		
Randomized Controlled Trials		
Blot, 1981[1] **RCT; France** **Baseline N=200** **Analytic N=109 (Attrition: 46%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: 27.5± 4.5y Race/Ethnicity: Origin: French 90%, Immigrants 10% • SES: ○ Occupation class of wife: Upper (I, II) 15%, Middle (III) 20%, Lower (32%), Other 8%, None 16%; ○ Occupation class of husband: Upper (I, II) 34%, Middle (III) 22%, Lower (32%), Other 11%, None 0% • Parity: 0: 54%, 1: 35.5%, 2: 5.5%, ≥ 3: 5% • Folate deficiency: Serum folate ≤4 µg/L: n=72 (36%), RBC folate <200 µg/L: n=52 (26%), MCV ≥100 fL: n=13 • GA at enrollment: 28wk • Source population: 11% in upper social classes (I and II), 56% in lower classes (III and IV)	**Exposure:** Folic acid supplementation from 28wk of gestation to delivery; 2 groups (N=200): • Fe: 105 mg Fe + 500 mg ascorbic acid (Ref, analytic N=55) • Fe+FA: 350 mg/d FA + 105 mg Fe + 500 mg ascorbic acid (analytic N=54)* All women consumed iron and ascorbic acid ***Authors report mg/d, but typo suspected*** *Exposure assessment method:* Double-blind; Each woman received 90 tablets, and instructed to take 1/d before breakfast until delivery. Mothers answered a questionnaire after delivery on treatment adherence and acceptability. **Outcome:** • Serum folate, RBC folate, Hemoglobin, MCV *Outcome assessment method:* Venous blood drawn at 28wk of gestation and at labor onset. Hemoglobin and red blood cell indices assessed using a Coulter counter. Competitive radioligand binding assay used to assess serum and total folate levels. RBC	**Confounders accounted for:** • Maternal age SES Parity **Not accounted for:** • Key confounders: Race/ethnicity, Anthropometry, Smoking • Other factors considered: Substance use **Limitations:** • Power analysis NR, 46% attrition • No preregistered data analysis plan

[viii] Values reported as mean± standard deviation, unless otherwise stated

[ix] BMI: body mass index; d: day; FA: folic acid; Fe: iron; GA: gestational age; GWG: gestational weight gain; HPLC: high performance liquid chromatography; MCV: mean corpuscular volume; mo: month(s); MTHF: methyltetrahydrofolate; MTHFR: methyltetrahydrofolate reductase; NIH: National Institutes of Health; NR: not reported; NS: non-significant; PCS: prospective cohort study; RBC: red blood cell; RCS: retrospective cohort study; RCT: randomized controlled trial; RDA: recommended daily allowance; SEM: standard error of the mean; SES: socioeconomic status; USDA: United States Department of Agriculture; wk: week(s); y: year(s)

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Serum folate at 28wk: social class IV (Mean=3.9 µg/L) < social class I (Mean=5 µg/L) **Funding Sources:** NR	folate determined as the difference between total and serum folate levels.	
Caudill, 1997[2] **RCT; United States** **Baseline N=12** **Analytic N=12 (Attrition: 0%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: Inclusion criterion: 18-35y • Folate deficiency: 0% • Smoking status: 0% • GWG: ~0.45 kg/wk • Substance use : No drug or alcohol use **Funding Sources:** NIH	**Exposure:** Folic acid from supplements during 14wk to 25wk of gestation; 2 groups • 330 µg/d (Ref, N=6) • 730 µg/d (N=6) All women consumed study-provided diet containing 120 µg/d folate. All women consumed a multivitamin supplement not including folic acid to provide, in combination with diet, RDA for all essential nutrients. *Exposure assessment method:* Commercially available folic acid used to prepare the folate supplements; content confirmed periodically via HPLC. **Outcome:** • Serum folate, RBC folate *Outcome assessment method:* Fasting venous blood collected into EDTA tubes at baseline and weekly thereafter for 12wk. Additional blood collected monthly in subsample. Samples stored at -20 °C until analysis. Serum and RBC folate concentrations determined microbiologically using *Lactobaccillus casei*.	**Confounders accounted for:** • Smoking **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, SES, Anthropometry, Parity • Other factors considered: **Limitations:** • No information about randomization • Little information on participant characteristics • Power analysis NR • No preregistered data analysis plan
Hekmatdoost, 2015[3] **RCT; Iran (Islamic Rep. of)** **Baseline N=220 (181 became pregnant within 6 mo)** **Analytic N=135 (Attrition: 38.6%, 25.4%)** **Power Analysis**: **n**=22 per group at 80% power to detect difference with a=0.05 in plasma folate of	**Exposure:** Folic acid supplementation during <6mo preconception through 20wk gestation; 2 groups: • 1 mg/d 5-MTHF (N=110 randomized, N=69 pregnancies) • 1 mg/d FA (N=110 randomized, N=66 pregnancies) *Exposure assessment method:*	**Confounders accounted for:** • Maternal age, Anthropometry **Not accounted for:** • Key confounders: Race/ethnicity, SES, Smoking, Parity • Other factors considered:

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
10 nmol/L. Included ten times additional samples to account for estimated loss to follow-up. **Baseline characteristics:** • Maternal age: Mean ~33.5y • MTHFR status: ○ 677CT: CC: n=109, CT: n=89, TT: n=22 ○ 1298AC: AA: n=152, AC: n=49, CC: n=19 • Prepregnancy BMI: ~29 • Substance use: Alcohol or drug abuse excluded • GA at enrollment: ≤6mo preconception • Plasma folate at baseline: Mean ~17.7 nmol/L • Previous spontaneous abortions: ~3.6, ≥3: 100% **Funding Sources:** Avicenna Research Institute and National Institute of Nutrition Research	Double blind RCT; Study visits occurred at baseline, after 8wk, and at gestational weeks 4, 8, 12, and 20. Supplements delivered every 4wk and participants instructed to return unused supplements at each visit. Adherence determined at each visit via pill counting and participants confirmed that capsules removed were taken as prescribed. Weekly telephone contacts encouraged adherence. **Outcome:** • Plasma folate *Outcome assessment method:* Folate concentrations in EDTA-treated plasma measured via immunoassay. MTHFR gene polymorphisms for C677T and A1298C evaluated at randomization.	**Limitations:** • The doses not described as the same dietary folate equivalent • Statistical tests unclear • Likely insufficient sample sizes for MTHFR polymorphism analyses No preregistered data analysis plan
Juarez-Vazquez, 2002[4] **RCT; Mexico** **Baseline N=371** **Analytic N=267 (Attrition: 28%)** **Power Analysis:** n=150 per group at 80% power with one-tailed α=0.05 to detect 3 g/dL mean increase in hemoglobin in both groups and additional 20% increase in test group. Assumes 10% drop-out rate. **Baseline characteristics:** • Maternal age: Mean ~25y • Parity: Gravidity ~1.7 • Substance use: Alcohol or drug addiction excluded • GA at enrollment: ~20.5wk (range: 14-27) • Iron deficiency anemia (hemoglobin <11 g/dL and serum ferritin <lower limit of lab range): 100%; • Weight at enrollment: ~59.5 kg	**Exposure:** Folinic acid supplementation for 60d between 14-27wk of gestation, 2 groups: • 80 mg Fe (Ref, N=182) • 0.370 mg folinic acid + 80 mg Fe (N=189) No women received any treatment (concomitant or in the previous 30d) which could have interfered with hematopoiesis. *Exposure assessment method:* Double-blind RCT; Both test and reference drugs were administered in two daily doses of drinkable vials for 60 days. **Outcome:** • Serum folate, Hemoglobin, MCV *Outcome assessment method:* Hemoglobin, full blood count, serum iron, transferrin saturation, ferritin and folate levels, evaluated at d30 (intermediate evaluation — data not shown) and at d60.	**Confounders accounted for:** • Maternal age, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES, Anthropometry, Smoking • Other factors considered: **Limitations:** • Attrition/group sample sizes less than power calculation • No preregistered analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Funding Sources: NR		
McNulty, 2013[5] **RCT; United Kingdom** **Baseline N=190** **Analytic N=119 (Attrition: 37%)** **Power Analysis:** n=60 per group at 80% power with a=0.05 to detect difference in homocysteine concentration of 0.5 mmol/L **Baseline characteristics:** • Maternal age: Mean ~28.6y • Race/Ethnicity: White: 100% • Parity: ~0.95 • MTHFR status: CC: 41.3%, CT: 44.5%, TT: 14.3% • Smoking status: 16.8% • Prepregnancy BMI: at 14 wk gestation: ~24.7 • GA at enrollment: 12.8wk **Funding Sources:** Northern Ireland Department for Employment and Learning	**Exposure:** Folic acid supplementation during 14-36wk gestation; 2 groups: • 0 µg/d FA (Ref, N=94) • 400 µg/d FA (N=90) All women took 400 µg/d FA supplements during the first trimester *Exposure assessment method:* Double-blind; Participants at 14wk stratified by tertiles of homocysteine concentrations, and women in each stratum randomly assigned to receive 400 mg FA/d or a placebo until delivery. FA and placebo tablets were identical in color, size, and shape. Supplements were distributed every 4wk in 7-d pillboxes. The number of unused tablets was recorded to monitor adherence. No mandatory FA fortification in this region, but FA-fortified foods regularly consumed by the majority of sample. **Outcome:** • Serum folate, RBC folate, Serum vitamin B_{12} *Outcome assessment method:* Nonfasting blood samples collected at 14wk and 36 wk gestation. All samples were refrigerated, processed, and stored at -80C for batch analysis at study end. Microbiological assays used; samples were analyzed blind, and quality control addressed with repeated analysis of stored batches of pooled samples that covered a wide range of values.	**Confounders accounted for:** • Maternal age, Race/ethnicity, Anthropometry, Smoking Status, Parity **Not accounted for:** • Key confounders: SES • Other factors considered: Substance use **Limitations:** • No preregistered data analysis plan
Shere, 2015[6] **RCT; Canada** **Baseline N=87** **Analytic N=37 (Attrition: 57%)**	**Exposure:** Folic acid supplementation during 3mo preconception through delivery; 2 groups: • 1.1 mg/d FA (Ref, Baseline N=45) • 5.0 mg/d FA (Baseline N=42)	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking Status, Parity **Not accounted for:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Power Analysis: n=20 per group at 85% power with a=0.05 to detect differences in risk reduction of neural tube defects of 40% **Baseline characteristics:** • Maternal age: Mean ~31y • Race/Ethnicity: ○ Caucasian: ~51% ○ Black: ~7% ○ Asian: ~8% ○ Hispanic: ~11% ○ South Asian: ~11% ○ Other: ~8% • SES: ○ Education: College 14%, University 46%, Post-graduate 30% High school 11% ○ Employment: Full-time 57%, Part-time 22%, Student 3%, Not employed 19% ○ Marital status: Single 5%, In a relationship 11%, Engaged 3%, Married 81% • Parity: 0: 62%, 1: 30%, 2: 8% • Smoking status: 5.4% • Prepregnancy BMI: Weight: ~67 kg • Substance use: Alcohol (socially): 32.4% • GA at enrollment: 3mo before conception to 6wk gestation **Funding Sources:** Duchesnay Inc., Blainville, Quebec	All women received: Calcium (300 mg), Vitamin B_{12} (12mg), and Vitamin D (250 IU), Beta carotene (2700 IU), Thiamine (3 mg), Riboflavin (3.4 mg), Vitamin E (30 IU), Vitamin C (120 mg), Niacinamide (20 mg), Pantothenic acid (5 mg), Magnesium (50 mg), Iodine (0.15 mg), Iron (35 mg as ferrous fumarate), Copper (2 mg), and Zinc (15 mg) *Exposure assessment method:* Open-label, 2-arm, randomized clinical trial. Post-randomization, study coordinator and participants were not blinded to the study drug. Supplements were same size and identical in the quantity of other vitamins and minerals, except folic acid. Women received a 3-month supply of assigned multivitamin at baseline and pills were replenished at clinic visits. Women advised to leave each missed tablet in blister pack, and to bring all blister packs with them to clinic visits and appointments. Adherence calculated by pill counts: ~95.9%. Mean adherence decreased in women planning a pregnancy for >3-4mo, and increased again upon discovery of a pregnancy. **Outcome:** • Plasma folate, RBC folate at baseline (3mo pre-conception to 6wk gestation), 6wk, 12wk, and 30wk gestation *Outcome assessment method:* Fasted blood samples collected in EDTA-vacutainer tubes, which were shielded from light and placed on ice, processed, and stored at -80C. RBC and plasma folate measured via chemiluminescent immunoassay.	• Key confounders: None • Other factors considered: None **Limitations:** • Randomization: difference between groups for plasma folate, no blinding post-randomization • Analytic n less than power calculation • No preregistered data analysis plan
Cohort Studies		
Holmes, 2005[7] **PCS; Ireland** **Baseline N=120**	**Exposure:** Folic acid supplement intake during 12 to 35wk of gestation; 2 groups:	**Confounders accounted for:** • Anthropometry, Smoking Status **Not accounted for:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Analytic N=101 (Attrition: 16%) **Power Analysis:** NR **Baseline characteristics:** • Maternal age: Mean± SD: 28.8y± 5.6 • MTHFR status: CC: 44.5%, CT: 41.6%, 12.9% • Smoking status: 30% • BMI: at 12wk: 25.3± 4.7 **Funding Sources:** Health and Personal Social Services Research and Development Office, U.K.; Abbott GmbH	• No FA: (Ref, n=10 at 12wk, n=74 at 20wk, n=71 at 35wk) • FA: (n=91 at 12wk, n=27 at 20wk, n=30 at 35wk) Dose and frequency NR *Exposure assessment method:* Participants questioned about use of vitamin and mineral supplements at each time-point, and any folic acid supplementation was noted. **Outcome:** • Plasma folate, RBC folate *Outcome assessment method:* Nonfasting blood collected into aluminum foil-wrapped EDTA tubes at 12, 20, and 35wk of gestation and in a subgroup at 3d postpartum. After centrifugation, plasma and red blood cell lysates stored at -70 °C until batch analysis at study end. Plasma and RBC folate assessed via microbiological assay.	• Key confounders: Maternal age, Race/ethnicity, SES, Parity • Other factors considered: Substance use **Limitations:** • No power calculation (low group n's) • Exposure status not well defined (dose, frequency NR) • Changes in exposure status over time • No preregistered analysis plan • Not clear if FA-containing multivitamin supplements were included in FA group
Koebnick, 2001[8] **PCS; Germany** **Baseline N=201** **Analytic N=109 (Attrition: 46%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: Mean ~30.2y • Parity: ~1.8; ~48% primiparous • Smoking status: ~9% • Prepregnancy BMI: ~22 **Funding Sources:** NR	**Exposure:** Folate supplementation at 9-12wk, 20-22wk, and/or 36-38wk gestation modeled continuously; based on dietary patterns: • Predominantly vegetarian diet, n=70 (ovo-lacto vegetarians: n=27; low meat eaters: n=43) • Average Western diet, n=39 *Exposure assessment method:* Folate supplementation assessed via questionnaire. Diet type and food folate based on validated semiquantitative FFQ for 4d in each trimester. No calculation of dietary folate equivalents for folate-enriched foods. Folate concentrations in fortified juices taken from producer's data. **Outcome:**	**Confounders accounted for:** • Maternal age, Anthropometry, Smoking Status, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES • Other factors considered: Substance use **Limitations:** • Start of exposure and follow-up does not coincide for most participants • Exposure data is self-report; dose unknown • Power analysis, analytic n NR • Missing data not accounted for • No preregistered data analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
	• Plasma folate, RBC folate, Incidence of folate deficiency *Outcome assessment method:* Overnight fasting, venous blood was drawn. Plasma was separated from RBCs and stored at ~4-7 °C. Plasma and RBC folate concentrations determined with a chemiluminescent competitive protein binding assay. Folate deficiency defined as RBC folate <320 nmol/L.	
Ozer, 2016[9] **RCS; Turkey** **Baseline N=397** **Analytic N=397 (Attrition: 0%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: ~26y • Parity: 1.2 • Smoking status: Excluded • Prepregnancy BMI: 24.8 • Substance use: alcohol abuse excluded • Infant born ≤37 wk gestation: Preterm birth: n=31 (7.8%) • GA at enrollment: 8wk • Prepregnancy serum iron (µg/dL, Mean± SD): No FA: 75.2±4.6; 400 µg/d FA: 87.5±9.1, p=0.04 **Funding Sources:** NR	**Exposure:** Folic acid supplementation; 2 groups: • No FA before or during pregnancy (Ref, n=294) • FA from preconception, 400 µg/d (n=103) *Exposure assessment method:* Women identified and grouped retrospectively according to the receipt of periconceptional folate supplementation. **Outcome:** • Serum folate, Hemoglobin, Incidence of folate deficiency *Outcome assessment method:* Serum folate concentrations measured using chemiluminescent immunoassay. Folate deficiency diagnosed if serum folate <4.5 ng/ml.	**Confounders accounted for:** • Maternal age, Anthropometry, Smoking Status, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES • Other factors considered: **Limitations:** • Start of follow up and exposure may not be the same for all participants • Methods are not well defined, and may not represent the exposure of interest • Not clear if FA-containing multivitamin supplements were included in FA group • No preregistered data analysis plan
Exposure During Lactation		
RCTs		
Houghton, 2006[10] **RCT; Canada** **Baseline N=69** **Analytic N=64 (Attrition: 7%)**	**Exposure:** Folic acid supplementation during 1-16wk postpartum; 3 groups: • Placebo (Ref, N=23) • 400 µg/d folic acid (N=24, not randomized)	**Confounders accounted for:** • Maternal age, SES, Smoking Status, Parity **Not accounted for:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Power Analysis: n=21 per group at 80% power with a=0.0167 to detect 1 SD difference in mean RBC folate between groups (delta=209 nmol/L; SD=225 nmol/L), based on Houghton's previous work among lactating adolescent mothers. n=26 per group in anticipation of a 20% attrition rate. **Baseline characteristics:** • Maternal age: Mean ~32y • SES: ○ Education: Community college or university degree: 93% ○ Annual Family Income: ≥$75,000/y: 76% • Parity: ~0.6 • MTHFR status: CC: ~9.3%, CT: ~9.7%, TT: ~4% • Smoking status: 0% • GA at enrollment: 36wk • Prenatal folic acid supplement (Mean± SD): 5-MTHF: 886± 273 µg/d, FA: 935± 229 µg/d, Placebo:948± 207 µg/d, P=NS **Funding Sources:** Merck Eprova AG (Schaffhausen, Switzerland); Natural Sciences & Engineering Research Council of Canada; Canadian Institute of Health Research Training Grant in Clinical Nutrition; Ontario Student Opportunity Trust Fund, The Hospital for Sick Children Foundation Scholarship Program	• 400 µg/d 5-MTHF (N=22) All women received a daily multivitamin and mineral supplement *Exposure assessment method:* Folate content of supplements was verified analytically. Supplemental folate intakes were determined by assessing the difference between the number of capsules dispensed at randomization (<1wk postpartum) and at 16wk postpartum. In addition, all women agreed not to consume any other folate-containing vitamin or mineral supplement during the course of the study. **Outcome:** • Plasma folate *Outcome assessment method:* Plasma was portioned for future folate analyses, and sodium ascorbate (1%, wt:vol) was added to samples to prevent the oxidation of folate. All samples were frozen immediately after processing and was stored at -80C.Plasma and RBC folate concentrations were measured by microbiological assay using the test organism *Lactobacillus rhamnoses*.	• Key confounders: Race/ethnicity, Anthropometry • Other factors considered: Substance use **Limitations:** • Randomization: FA group recruited separately, not randomized, differences in baseline RBC and plasma folate among groups • Subsample results (RBC form and unmetabolized folic acid distributions) may be under-powered. • No preregistered data analysis plan
Keizer, 1995[11] **RCT; Canada** **Baseline N=29** **Analytic N=29 (Attrition: 0%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: ~17.0y, SEM=0.17 (range 14.0-19.0y)	**Exposure:** Folic acid supplementation during 1-12 wk postpartum; 2 groups • Placebo (Ref, N=15) • 300 µg folic acid/d (FA, N=14) *Exposure assessment method:* Double-blind RCT; Research assistants and participants were unaware of the capsule contents, and the supplements were visually indistinguishable. Women	**Confounders accounted for:** **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, SES, Anthropometry, Smoking, Parity • Other factors considered: **Limitations:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Race/Ethnicity: ○ White: 92% ○ Native Canadian/White: 4% ○ Black: 3% ○ Asian/White: 1% • SES: ○ Predominantly low SES ○ Main source of income: Government: 56%, Parent or guardian: 39%, Employment: 5% • Folate deficiency: 59% consumed <67% of recommended nutrient intake • Substance use: Negligible • Infant born ≤37wk of gestation: 0% • Hb ≥110g/L at 36wk of gestation: 100% **Funding Sources:** Natural Sciences and Engineering Research Council of Canada	were instructed to avoid the consumption of additional vitamin and mineral supplements during the postpartum period. Adherence was calculated by determining the difference in the number of capsules provided at the beginning and those remaining at the end of each 4-wk period. **Outcome:** • Plasma folate, RBC folate, Serum vitamin B_{12}, Hemoglobin *Outcome assessment method:* Fasted venous blood collected at 36wk of gestation and 4, 8, and 12wk postpartum. Complete blood cell counts obtained by Coulter Counter. Plasma, RBC folate, and plasma B_{12} determined by competitive binding radioassay.	• No information on missing data for continuous outcomes or multiple analyses • No preregistered data analysis plan
Mackey, 1999[12] **RCT; United States** **Baseline N=42** **Analytic N=42 (Attrition: 0%)** **Power Analysis:** NR **Baseline characteristics:** • Maternal age: Mean ~34y (range: 26-42y) Race/Ethnicity: White: 100% • SES: ○ Maternal education: ~16y ○ Socioeconomic status: ~72 (scores 60-79 associated with professional, technical, and managerial workers) • Parity: 2 • BMI at 3mo postpartum (baseline): ~25 • Maternal weight at 3mo postpartum (baseline): ~67kg • Prenatal FA supplement: ~0.9 mg/d	**Exposure:** Folic acid from supplements during 3mo to 6mo postpartum; 2 groups • 0 mg/d (Ref, N=21) • 1 mg/d (N=21) All women received a multivitamin and mineral supplement that contained: 2500 IU vitamin A, 60 mg vitamin C, 400 IU vitamin D as ergocalciferol, 30 IU vitamin E, 1.5 mg thiamine, 1.7 mg riboflavin, 20 mg niacinamide, 2 mg vitamin B-6, 6 mg vitamin B-12, 300 mg biotin, 10 mg pantothenic acid, 9 mg Fe, 150 mg I, 3 mg Zn, 2.5 mg Mn, 25 mg Cr, and 25 mg Mo. *Exposure assessment method:* Adherence defined as taking >80% of monthly allotments of folic acid supplementation. **Outcome:** • Plasma folate, RBC folate, Hemoglobin, MCV	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking Status, Parity **Not accounted for:** • Key confounders: • Other factors considered: Substance use **Limitations:** • Power analysis NR • No preregistered analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Funding Sources: USDA	*Outcome assessment method:* Blood was drawn into tubes containing EDTA, handled under gold light and stored at -70C until analyzed. Hemoglobin and MCV measured via complete blood count. Plasma and erythrocyte folate were measured by a microbiological assay with *Lactobacillus casei*.	
Cohort Study		
Houghton, 2007[13] **PCS nested in RCT; Canada** **Baseline N=69** **Analytic N=53 (Attrition: 23%)** **Baseline characteristics:** *See Houghton, 2006* **Funding Sources:** *See Houghton, 2006*	**Exposure:** Folic acid supplementation during 1-16wk postpartum All women received a daily multivitamin and mineral supplement *Exposure assessment method:* Folate content of supplements was verified analytically. Supplemental folate intakes were determined by assessing the difference between the number of capsules dispensed at randomization (<1wk postpartum) and at 16wk postpartum. In addition, all women agreed not to consume any other folate-containing vitamin or mineral supplement during the course of the study. Synthetic folate = (µg from supplement) + (µg from fortification) Dietary folate intakes estimated with 3d weighed food records completed over 2 nonconsecutive days and 1 weekend day. Participants were trained by registered dietitians to complete food records using an electronic digital scale accurate to 1 g. Dietary folate intakes tabulated from the diet records using Health Canada's Canadian Nutrient File, based on USDA Nutrient Database for Standard Reference. Dietary folate reported as (1) total dietary folate (sum of naturally occurring folate and folic acid added as fortificant) and (2) folic acid, as a fortificant, separately. **Outcome:** • Plasma folate	**Confounders accounted for:** • Maternal age, SES, Smoking Status, Parity **Not accounted for:** • Key confounders: Race/ethnicity, Anthropometry • Other factors considered: Substance use **Limitations:** • Subsample results (RBC form and unmetabolized folic acid distributions) may be under-powered. • No information on distribution of missing data or robustness of results despite missing data • No preregistered data analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
	Outcome assessment method: *See Houghton, 2006*	
Uncontrolled Before-and-After Study		
Tamura, 1980[14] **Uncontrolled Before-and-After; Japan** **Baseline N=16** **Analytic N=16 (Attrition: 0%)** **Power Analysis:** NR **Baseline characteristics:** • SES: All women belonged to the same socioeconomic group • Mothers were apparently healthy and had no history of any serious diseases **Funding Sources:** United States-Japan Medical Cooperation Program	**Exposure:** Maternal intake of 1mg/d synthetic folic acid (PteGlu) for 4 wk, starting 3-25wk postpartum in lactating mothers (n=16) *Exposure assessment method:* NR **Outcome:** • Plasma folate, RBC folate *Outcome assessment method:* Folate levels were determined by microbiological assay using *L. casei*.	**Confounders accounted for:** • SES **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, Anthropometry, Smoking, Parity • Other factors considered: Substance use **Limitations:** • No control group; Intervention methods/adherence NR • Statistical analysis NR • Power analysis NR

Table 3. Results from studies that examined the relationship between folic acid intake from dietary supplements and/or fortified foods during pregnancy and lactation and micronutrient status[x, xi]

Study	Intervention/Exposure	Outcome and Results
Exposure Before and/or During Pregnancy		
Randomized Controlled Trials		
Blot, 1981[1] **RCT; France** **Summary:** Consuming folic acid plus iron supplements compared to iron alone during the third trimester of pregnancy resulted in higher serum and RBC folate at delivery but did not affect hemoglobin or MCV. **Limitations:** • Power analysis NR, 46% attrition • No preregistered data analysis plan	Folic acid supplementation from 28 wk of gestation to delivery; 2 groups (N=200): • Fe: 105 mg Fe + 500 mg ascorbic acid (Ref, analytic n=55) • FA+Fe: 350 mg/d FA + 105 mg Fe + 500 mg ascorbic acid (analytic n=54)* All women consumed iron and ascorbic acid ***Authors report mg/d, but typo suspected***	**Serum folate (µg/L, Geometric mean (range, when provided)), Mann-Whitney U Test** • 28wk (data pooled): 5.0 (<1-25), P=NS • Delivery: ○ Fe: 4.8 ○ **FA+Fe: 7.4, P<0.001** • Note: rise in serum folate only occurred when baseline <6 µg/L; mean rise: Fe: 0.5 µg/L, FA+Fe: 3 µg/L (P=NR) **RBC folate (µg/L, Geometric mean (range, when provided)), Mann-Whitney U Test** • 28wk (data pooled): 248 (55-612), P=NS • Delivery: ○ Fe: 362 ○ **FA+Fe: 483, P<0.01** **Hemoglobin (g/100 mL, Mean± SD (range, when provided)), Mann-Whitney U Test** • 28wk (data pooled): 12.3± 0.9 (7.7-15), P=NS • Delivery: ○ Fe: 14.0±1.1 ○ FA+Fe: 14.1±1.0, P=NS

[x] ANCOVA: analysis of covariance; ANOVA: analysis of variance; CI: confidence interval; d: day; FA: folic acid; Fe: iron; GEE: generalized equation estimataing; IQR: interquartile range; MCV: mean corpuscular volume; mo: month(s), MTHF: methyltetrahydrofolate; MTHFR: methyltetrahydrofolate reductase; NR: not reported; NS: non-significant; PCS: prospective cohort study; Q#: quartile; RBC: red blood cell; RCS: retrospective cohort study; RCT: randomized controlled trial; RDA: recommended daily allowance; SD: standard deviation; SE: standard error; SEM: standard error of the mean; THF: tetrahydrofolate; wk: week(s)

[xi] Statistically significant findings bolded

Study	Intervention/Exposure	Outcome and Results
		MCV (fL, Mean± SD (range, when provided)), Mann-Whitney U Test • 28wk (data pooled): 94.2± 4.7 (62-104), P=NS • Delivery: ○ Fe: 95.5±3.6 • FA+Fe: 95.5±3.7, P=NS
Caudill, 1997[2] **RCT; United States** **Summary:** Consuming 330 µg/d vs 730 µg/d folic acid supplements from 14-25wk gestation resulted in higher serum folate at steady state and 3mo postpartum, but did not affect RBC folate. **Limitations:** • No information about randomization • Little information on participant characteristics • Power analysis NR • No preregistered data analysis plan	Folic acid from supplements during 14wk to 25wk gestation; 2 groups • 330 µg/d (Ref, N=6) • 730 µg/d (N=6) All women consumed study-provided diet containing 120 µg/d folate. All women consumed a multivitamin supplement not including folic acid to provide, in combination with diet, RDA for all essential nutrients	**Serum folate (nmol/L, Mean± SD)** • at baseline, ANOVA, P=NS ○ 330 mg/d FA: 51±19 ○ 730 mg/d FA: 46±22 • at steady state, ANOVA, P≤0.05 ○ 330 mg/d FA (Study week 8): 27±9 ○ **730 mg/d FA (Study week 1): 45±13** • at 3mo postpartum, Significance test NR ○ 330 mg/d FA: 34± 14 ○ 730 mg/d FA: 48± 14 **RBC folate (nmol/L, Mean± SD)** • at baseline, ANOVA, P=NS ○ 330 mg/d FA (n=4): 1383± 158 ○ 730 mg/d FA (n=4): 1174±352 • at steady state, ANOVA, P=NS ○ 330 mg/d FA (Study week 1): 1453±252 ○ 730 mg/d FA (Study week 7): 1734±209 • at 3mo postpartum, Significance test NR ○ 330 mg/d FA (n=4): 1306±272 ○ 730 mg/d FA (n=4): 1706±220
Hekmatdoost, 2015[3] **RCT; Iran (Islamic Rep. of)** **Summary:** Consuming either 1 mg/d folic acid or 1 mg/d 5-MTHF from <6mo preconception through 20wk gestation resulted in higher serum folate compared to baseline. Consuming 5-MTHF resulted in a greater increase in serum folate over time than folic acid.	Folic acid supplementation <6mo through 20wk gestation, 2 groups: • 1 mg/d 5-MTHF (N=110 randomized, n=69 pregnancies) 1 mg/d FA (N=110 randomized, n=66 pregnancies)	**Plasma folate increased significantly in both groups over time; 5-MTHF > folic acid (value=2.39, P<0.01)** Plasma folate by MTHFR polymorphism, Test unclear • Note: No TTAC participants in MTHF group presented • Ref: CCAA • **TTAA: value= -0.98, SE=0.52, P=0.05** • All other genotypes: P=NS Serum folate, Mixed regression model with all predictors • R^2 = 0.93, SD of random effect for:

Study	Intervention/Exposure	Outcome and Results
Limitations: • The doses not described as the same dietary folate equivalent • Statistical tests unclear • Likely insufficient sample sizes for MTHFR polymorphism analyses • No preregistered data analysis plan		• Intercept: 0.0031 • Time: 0.0059 • Residual: 0.0019 Change in serum folate over time, Test unclear • Note: No TTAC participants • Ref: CCAA • CCAC: P=0.056 • CTAA: P=0.051 • **TTAA: P<00.1 (typo in paper)** All other genotypes: P=NS
Juarez-Vazquez, 2002 **RCT; Mexico** **Summary:** Consuming 0.370 mg/d folinic acid plus 80 mg/d iron supplements for 60 d during mid-pregnancy resulted in greater increases in hemoglobin compared to 80 mg/d iron alone, but did not affect serum folate or MCV. **Limitations:** • Attrition/group sample sizes less than power calculation • No preregistered analysis plan	Folinic acid supplementation for 60d between 14 to 27wk of gestation, 2 groups: • 80 mg Fe (Ref, N=182) • 0.370 mg folinic acid + 80 mg Fe (N=189) • No women received any treatment (concomitant or in the previous 30 days) which could have interfered with haematopoiesis.	**Serum folate (Mean± SD, ng/mL), Mixed repeated-measure linear regression** • Fe: ○ Baseline: 10.4±13.6 ○ 60d: 8.4± 4.7 • FA+Fe: ○ Baseline: 13.9±46.4 ○ 60d: 10.2±4.64 **Hemoglobin (Mean± SD, g/dL), Mixed repeated-measure linear regression, P<0.005 between treatments at 60d** • Fe: ○ Baseline: 10.37±0.94 ○ **60d: 11.17±1.51; P<0.001** • FA+Fe: ○ Baseline: 10.16±0.96 ○ **60d: 11.58±1.7; P<0.001** **MCV (Mean± SD, pg), Mixed repeated-measure linear regression** • Fe: ○ Baseline: 86.4±8.6 ○ 60d: 86.5±8.6 • FA+Fe: ○ Baseline: 85.4±9.4 ○ 60d: 87.6±9

Study	Intervention/Exposure	Outcome and Results
		Per-protocol subanalysis among 64 women with the lowest quartile of baseline hemoglobin (Mean=8.96, Range= 5.9–9.8 g/dL) • **Increase in hemoglobin (g/dL) from baseline to 60d, Multivariable regression analysis, P=0.07** • Fe (n=30): 0.5±0.5 • FA+Fe (n=34): 2.3±0.53
McNulty, 2013[5] **RCT; United Kingdom** **Summary:** Consuming 400 µg/d folic acid supplements throughout pregnancy compared to only during the first trimester of pregnancy resulted in higher serum folate and RBC folate at 36wk gestation. There was no difference in serum vitamin B_{12}. **Limitations:** • No preregistered data analysis plan	Folic acid supplementation during 14 to 36wk of gestation; 2 groups: • 0 µg/d FA (Ref, N=94) • 400 µg/d FA (N=90) All women took 400 µg/d FA supplements during the first trimester	**Serum folate (nmol/L, Mean± SD), Paired t-test** • 0 µg/d FA: ○ **14wk: 45.7± 21.3** ○ **36wk: 19.5± 16.5, P<0.001** • 400 µg/d FA: ○ 14wk: 47.0± 21.0 ○ 36wk: 48.2± 22.9, P=0.791 **Change in serum folate (nmol/L, Mean± SD), repeated-measures ANOVA, Time*Treatment, P<0.001** • 0 µg/d FA: -26.1± 19.0 • 400 µg/d FA: 0.9± 24.7 **RBC folate (nmol/L, Mean± SD), Paired t-test** • 0 µg/d FA: ○ **14wk: 1107± 747** ○ **36wk: 873± 377, P<0.001** • 400 µg/d FA: • **14wk: 1203± 639** • **36wk: 1746± 683, P<0.001** **Change in RBC folate (nmol/L, Mean± SD), repeated-measures ANOVA, Time*Treatment, P<0.001** • 0 µg/d FA: -250± 690 • 400 µg/d FA: 549± 661 **Serum B_{12} concentrations** decreased significantly in both groups from 14wk - 36wk (P<0.001); no treatment effect (data NR)

Study	Intervention/Exposure	Outcome and Results
Shere, 2015[6] **RCT; Canada** **Summary:** Consuming FA supplements from ≤3mo before pregnancy resulted in higher RBC folate concentrations at 6, 12, and 30wk gestation, with a greater increase in RBC folate among women taking 5 mg/d FA compared to 1.1 mg/d FA. Across both supplement groups (1.1 and 5 mg/d), plasma folate increased from baseline to 6wk of gestation, then decreased through 30wk of gestation. Women who supplemented with 1.1 mg/d FA had higher plasma folate levels at baseline and 12wk of gestation, but there was no difference between the groups at 30wk of gestation. **Limitations:** • Randomization: difference between groups for plasma folate, no blinding post-randomization • Analytic n less than power calculation • No preregistered data analysis plan	Folic acid supplementation during 3mo preconception through delivery; 2 groups: • 1.1 mg/d FA (Ref, Baseline N=45) • 5.0 mg/d FA (Baseline N=42) All women received: Calcium (300 mg), Vitamin B_{12} (12mg), and Vitamin D (250 IU), Beta carotene (2700 IU), Thiamine (3 mg), Riboflavin (3.4 mg), Vitamin E (30 IU), Vitamin C (120 mg), Niacinamide (20 mg), Pantothenic acid (5 mg), Magnesium (50 mg), Iodine (0.15 mg), Iron (35 mg as ferrous fumarate), Copper (2 mg), and Zinc (15 mg)	**RBC folate (nM), mixed-model repeated measures ANOVA, Dose*Time interaction: F(3,105) = 9.471, P <0.001**, partial nu2 =0.213 **RBC folate (nM): between group differences, Bonferroni adjusted pairwise comparison** • at 6wk: 1.1 mg < 5 mg (P=NS) • **at 12wk: 1.1 mg < 5 mg (P=0.03)** • **at 30wk: 1.1 mg < 5 mg (P=0.001)** **RBC folate (nM): within-group change over time, Bonferroni adjusted pairwise comparison** • **1.1 mg FA: P<0.001, with increases from:** ○ **Baseline to: 6wk (P<0.001), 12wk (P<0.001), 30wk (P<0.001)** ○ **12wk to 30wk (P=0.044)** • **5 mg FA: P<0.001, with increases from:** ○ **Baseline to: 6wk (P<0.001), 12wk (P<0.001), 30wk (P<0.001)** ○ **6wk to 30wk (P=0.001)** ○ **12wk to 30wk (P=0.002)** **Plasma folate (nM), mixed-model repeated measures ANOVA,** Dose*Time interaction: F(3,108) = 0.905, P=0.44, partial nu2 =0.025; **Time (main effect): P<0.001; Dose (main effect): P=0.027** **Plasma folate (nM): between group difference, Mann Whitney U Test** • at baseline: **1.1 mg FA > 5 mg FA (P=0.013)** • at 6wk: 1.1 mg FA > 5 mg FA (P=NS) • at 12wk: **1.1 mg FA > 5 mg FA (P=0.007)** • at 30wk: 1.1 mg FA > 5 mg FA (P=NS) **Plasma folate (nM): within-group change over time, Bonferroni adjusted pairwise comparison** • **1.1 mg FA: P<0.001, with increases from:** ○ **Baseline to: 6wk (P=0.024), 12wk (P=0.004),** 30wk (P=NS) • **5 mg FA: P<0.001, with increases from:** ○ **Baseline to 6wk (P=0.037), 12wk (P=0.011),** 30wk (P=NS)

Study	Intervention/Exposure	Outcome and Results
		In both 1.1 mg FA and 5 mg FA groups, Plasma folate concentrations increased from baseline to 6wk gestation and decreased over the course of pregnancy, with a faster rate of decrease in the 5 mg group from 6 to 12wk. (data NR)
Cohort Studies		
Holmes, 2005[7] **PCS; Ireland** **Summary:** Consuming folic acid supplements during 12-35 wk of gestation was associated with higher plasma folate and RBC folate at 12, 20, and 35 wk of gestation, as well as higher plasma folate at 3d postpartum, compared with pregnant women who did not take folic acid supplements. There was no association between folic acid supplementation and RBC folate at 3d postpartum. **Limitations:** • Key confounders NOT accounted for: Maternal age, Race/ethnicity, SES, Parity • No power calculation (low group n's) • Exposure status not well defined (dose, frequency NR) • Changes in exposure status over time • No preregistered analysis plan • Not clear if FA-containing multivitamin supplements were included in FA group	Folic acid supplement intake during 12-35 wk of gestation; 2 groups: • No FA: (Ref, n=10 at 12wk, n=74 at 20wk, n=71 at 35wk) • FA: (n=91 at 12wk, n=27 at 20wk, n=30 at 35wk) Dose and frequency NR	**Plasma folate (µg/L, Mean± SD [n])** • at 12 wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 6.83± 3.83 [10] ○ **FA: 19.12± 15.08 [91]** • at 20 wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 6.60± 2.56 [74] ○ **FA: 12.15± 6.63 [27]** • at 35wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 6.20± 4.48 [71] ○ **FA: 13.41± 7.32 [30]** • at 3d postpartum, Repeated-measures ANOVA, P<0.05 ○ No FA: 6.05± 2.52 [15] ○ **FA: 12.62± 4.58 [6]** **RBC Folate (µg/L, Mean± SD [n])** • at 12 wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 306± 78 [10] ○ **FA: 560± 226 [91]** • at 20 wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 486± 193 [74] ○ **FA: 678± 333 [27]** • at 35 wk, Repeated-measures ANOVA, P<0.05 ○ No FA: 403± 173 [71] ○ **FA: 689± 351 [30]** • at 3d postpartum, Repeated-measures ANOVA, P=NS ○ No FA: 438 769 [15] FA: 665±427 [6]
Koebnick, 2001[8] **PCS; Germany** **Summary:** Consuming folic acid supplements during pregnancy was associated with higher	Folate supplementation at 9-12wk, 20-22wk, and/or 36-38wk gestation modeled continuously; based on dietary patterns: • Predominantly vegetarian diet, n=70 (ovo-lacto vegetarians: n=27; low meat eaters: n=43)	**Plasma folate (nmol/L, B± SE), GEE** • **Supplemental folate (mg/d): 0.02± 0.01, P<0.0001** • **Folate from multivitamin fortified juices (mg/d): 0.001± 0.0004, P=0.046** **RBC folate (nmol/L, B± SE), GEE**

Study	Intervention/Exposure	Outcome and Results
plasma and RBC folate, but not with risk of folate deficiency. **Limitations:** • Key confounders NOT accounted for: Race/ethnicity, SES • Start of exposure and follow-up does not coincide for most participants • Exposure data is self-report; dose unknown • Power analysis, analytic n NR • Missing data not accounted for • No preregistered data analysis plan	Average Western diet, n=39	• **Supplemental folate (mg/d): 0.22± 0.07 P=0.003** • **Folate from multivitamin fortified juices (mg/d): 0.8± 0.4, P=0.04** **Folate deficiency (nmol/L, OR (95% CI)), GEE** • Supplemental folate (mg/d): 0.99 (0.99, 0.99) • Folate from multivitamin fortified juices (mg/d): 0.98 (0.95, 1.01)
Ozer, 2016[9] **RCS; Turkey** **Summary:** There was no difference in serum folate, folate deficiency, and hemoglobin from before pregnancy to the first trimester of pregnancy in women supplemented with 400 µg/d folic acid during the periconceptional period. There was no difference in serum folate, folate deficiency, and hemoglobin between women supplemented with 400 µg/d folic acid during the periconception and those not supplemented with folic acid. **Limitations:** • Not all key confounders accounted for • Start of follow up and exposure may not be the same for all participants • Methods are not well defined, and may not represent the exposure of interest	Folic acid supplementation; 2 groups: • No FA before or during pregnancy (Ref, N=294) • FA from preconception, 400 µg/d (N=103)	**Serum folate (ng/mL), Student t test or Mann-Whitney U test:** • Prepregnancy, P=0.072 ○ No FA: 10.0± 6.5 ○ 400 µg/d FA: 9.8± 4.7 • Pregnancy, P=0.061 ○ No FA: 9.2± 4.4 ○ 400 µg/d FA: 10.9± 3.7 • No FA: Prepregnancy vs Pregnancy, P=0.059 • 400 µg/d FA: Prepregnancy vs Pregnancy, P=0.057 **Folate deficiency (<4.5 ng/mL), Student t test or Mann-Whitney U test:** • Prepregnancy, P=0.828 ○ No FA: n=21 (7.4%) ○ 400 µg/d FA: n=8 (7.8%) • Pregnancy, P=0.831 ○ No FA: n=22 (7.5%) ○ 400 µg/d FA: n=6 (5.8%) **Hemoglobin (g/dL), Student t test or Mann-Whitney U test:** • Prepregnancy, P=0.544 ○ No FA: 11.9± 2.9 ○ 400 µg/d FA: 12.4± 2.1 • Pregnancy, P=0.549

Study	Intervention/Exposure	Outcome and Results
• Not clear if FA-containing multivitamin supplements were included in FA group • No preregistered data analysis plan		○ No FA: 11.8± 3.1 ○ 400 µg/d FA: 12.1± 2.2
Exposure During Lactation		
RCTs		
Houghton, 2006[10] **Canada** **Summary:** Women who supplemented with 5-MTHF and FA during lactation had no difference in RBC folate at 4wk postpartum. At 16wk postpartum, women who supplemented with 5-MTHF had higher RBC folate than who supplemented with folic acid or no supplementation. At 4 and 16wk postpartum, mean plasma folate was greater in women who supplemented with either 5-MTHF and folic acid during lactation compared to women who did not use supplements. **Limitations:** • Randomization: FA group recruited separately, not randomized, differences in baseline RBC and plasma folate among groups • Subsample results (RBC form and unmetabolized folic acid distributions) may be under-powered. • No preregistered data analysis plan	Maternal intake of folic acid from supplements, 1-16wk postpartum; 3 groups: • Placebo (Ref, N=23) • 400 µg/d folic acid (N=24, not randomized) • 400 µg/d 5-MTHF (N=22)	**Plasma folate (nmol/L): Geometric Mean (95% CI); Repeated measures ANCOVA, main effects of treatment (P<0.0001) and time (P<0.02)** • Placebo (n=22): ○ Baseline: 80.5 (68.3, 94.9) ○ 4wk postpartum: 58.0 (46.9, 71.8) ○ 16wk postpartum: 43.5 (34.8, 54.4) • FA (n=21): ○ Baseline: 102.3 (87.5, 119.5) ○ 4wk postpartum 112.6 (93.8, 135.1) ○ **16wk postpartum 93.5 (83.1, 105.2), vs placebo, P<0.002** • 5-MTHF (n=21): ○ Baseline 85.0 (72.3, 99.9) ○ 4wk postpartum 93.0 (78.7, 110.0) ○ **16wk postpartum 91.1 (71.2, 116.4), vs placebo, P<0.0001** **Total RBC (nmol/L), Mean (95% CI), Repeated ANCOVA with adjustment for baseline values** • Placebo (n=7): ○ Baseline: 2929 (2480, 3379) ○ 16wk: 1656 (1045, 2268) • FA (n=6): ○ Baseline: 3641 (2610, 4671) ○ 16wk: 1891 (1515, 2266) • 5-MTHF (n=7): ○ Baseline: 2914 (2353, 3475) ○ 16wk: 2193 (1801, 2585) • **16wk: 5-MTHF vs placebo and FA groups, P<0.03** **RBC folate (nmol/L), Geometric Mean (95% CI); Repeated ANCOVA, baseline RBC folate as a covariate: treatment*group interaction (P<0.01)**

Study	Intervention/Exposure	Outcome and Results
		• Placebo (n=22): ○ Baseline: 2453 (2162, 2785) ○ 4wk postpartum: 2188 (1891, 2532) ○ 16wk postpartum: 1390 (1198, 1613); **vs 4wk, P<0.0001** • FA (n=21): ○ Baseline: 3635 (3161, 4179) ○ 4wk postpartum: 3229 (2729, 3848) ○ 16wk postpartum: 1967 (1628, 2377); **vs 4wk, P<0.0001** • 5-MTHF (n=21): ○ Baseline: 2998 (2459, 3655) ○ 4wk postpartum: 2750 (2308, 3277) ○ 16wk postpartum: 2178 (1854, 2559); **vs 4wk, P<0.05; vs FA 16 wk, P<0.05; vs Placebo, P<0.002** • Author note: the decrease in status across time is likely due to the discontinuation of prenatal supplements, which contained 800-1000 µg/d folic acid. **THF (nmol/L), Mean (95% CI), Repeated ANCOVA with adjustment for baseline values** • Placebo (n=7): ○ Baseline: 1218 (752, 1683) ○ 16wk: 1068 (611, 1524) • FA (n=6): ○ Baseline: 1998 (278, 4219) ○ 16wk: 1517 (0, 3181) • 5-MTHF (n=7): ○ Baseline: 2044 (1167, 2920) ○ 16wk: 1010 (432, 1589) **5-MTHF (nmol/L), Mean (95% CI), Repeated ANCOVA with adjustment for baseline values** • Placebo (n=7): ○ Baseline: 601 (408, 793) ○ 16wk: 630 (469, 791) • FA (n=6): ○ Baseline: 630 (363, 896) ○ 16wk: 448 (358, 538) • 5-MTHF (n=7): ○ Baseline: 522 (393, 650)

Study	Intervention/Exposure	Outcome and Results
		○ 16wk: 573 (363, 783) **5-formylTHF (nmol/L), Mean (95% CI), Repeated ANCOVA with adjustment for baseline values** • Placebo (n=7): ○ Baseline: 186 (51, 320) ○ 16wk: 208 (141, 275) • FA (n=6): ○ Baseline: 316 (260, 373) ○ 16wk: 368 (299, 438) • 5-MTHF (n=7): ○ Baseline: 338 (270, 406) ○ 16wk: 239 (121, 357) • **16wk: FA vs placebo and 5-MTHF, P<0.03** **Unmetabolized folic acid (nmol/L), Mean (95% CI), Repeated ANCOVA with adjustment for baseline values** • Placebo (n=7): ○ Baseline: 19 (1, 57) ○ 16wk: 13 (2, 33) • FA (n=6): ○ Baseline: 25 (3, 70) ○ 16wk: 46 (19, 85) • 5-MTHF (n=7): ○ Baseline: 13 (4, 29) ○ 16wk: 24 (2, 70)
Keizer, 1995[11] **RCT; Canada** **Summary:** Consumption of 300 µg/d folic acid supplement from 1 -12 weeks postpartum was associated with RBC folate maintenance vs decline in placebo and maintenance in suboptimal plasma folate vs increase in placebo from 4 to 12 wk postpartum. FA supplementation did not affect mean plasma folate, plasma	Folic acid supplementation during 1-12 wk postpartum; 2 groups • Placebo (Ref, N=15) • 300 µg folic acid/d (FA, N=14)	**RBC Folate (nmol/L):** • FA, Mean (SEM) ○ 4wk: 796.0 (48.2) ○ 8wk: 801.8 (58.9) ○ 12wk: 690.7 (68.4) ○ 4wk vs 8wk vs 12wk, P=NS • Placebo, Mean ○ 4wk: 1023.2 ○ 8wk: (Value NR, but <1023.2 and >709.2) ○ 12wk: 709.2 ○ **4wk vs 8wk vs 12wk, P <0.05** • **FA vs Placebo at 4wk, P<0.05**

Study	Intervention/Exposure	Outcome and Results
vitamin B_{12}, hemoglobin, or milk folate concentrations. **Limitations:** • No information on missing data for continuous outcomes or multiple analyses • No preregistered data analysis plan		**Plasma folate <13.6 nmol/L (n, %)** • FA: ○ Baseline: 2 of 13 (15.4%) ○ Postpartum: 2 of 14 (13.3%) • Placebo: ○ Baseline: 2 of 13 (15.4%) ○ Postpartum: 6 of 15 (40.0%) **Plasma folate (nmol/L), Mean (SEM):** • 4wk: 21.8 (3.1), Median=18.6, IQR=9.5, 30.2 • 8wk: 18.0 (3.8), Median=19.0, IQR=9.7, 28.3 • 12wk: 17.2 (3.9), Median=18.6, IQR=9.8, 26.3 • 4wk vs 8wk vs 12wk, P=NS, No differences between groups **Plasma B_{12} (pmol/L, Mean (SEM)):** • 4wk: 283.3 (7.9), Median=258.4, IQR=208.9, 356.5 • 8wk: 276.0 (9.8), Median=263.7, IQR=191.2, 314.1 • 12wk: 254.6 (10.6), Median=237.6, IQR=192.8, 284.1 • 4wk vs 8wk vs 12wk, P=NS, No differences between groups **Hemoglobin (g/L, Mean (SEM)):** • 4wk: 133.4 (1.1), Median=134.0, IQR=127.5, 141.0 • 8wk: 133.1 (1.4), Median=134.0, IQR=129.0, 138.0 • 12wk: 133.3 (1.5), Median=134.0, IQR=129.0, 139.0 • 4wk vs 8wk vs 12wk, P=NS, No differences between groups
Mackey, 1999[12] **RCT; United States** **Summary:** Taking 1 mg/d folic acid from 3 to 6 mo postpartum in lactating women increased RBC folate and hemoglobin, but did not effect plasma folate or MCV. **Limitations:** • Power analysis NR • No preregistered analysis plan	Folic acid from supplements during 3mo to 6mo postpartum; 2 groups • 0 mg/d (Ref, N=21) • 1 mg/d (N=21) All women received a multivitamin	**Plasma folate (nmol/L; Mean±SEM), ANCOVA, P=NS** • 0 mg/d FA: ○ 3mo: 42.1±5.1 ○ 6mo: 36.8±4.2 • 1 mg/d FA: ○ 3mo: 44.9±4.1 ○ 6mo: 47.6±6.5 **RBC folate (nmol/L; Mean±SEM), ANCOVA, P<0.05 between groups at 6mo** • 0 mg/d FA: ○ 3mo: 731.0±58.5

Study	Intervention/Exposure	Outcome and Results
		○ 6mo: 667.3±52.3 • 1 mg/d FA: ○ 3mo: 823.8±61.7 ○ 6mo: 840.2±49.5 **Hemoglobin (g/L; Mean±SEM), ANCOVA, P<0.02 between groups at 6mo** • 0 mg/d FA: ○ 3mo: 134± 2 ○ 6mo: 134± 2 • 1 mg/d FA: ○ 3mo: 138± 1 ○ 6mo: 140± 1 **MCV (fL; Mean±SEM), ANCOVA, P=NS** • 0 mg/d FA: ○ 3mo: 87.3± 1.7 ○ 6mo: 87.0± 1.6 • 1 mg/d FA: ○ 3mo: 88.4± 0.8 6mo: 88.3± 0.6
Cohort Study		
Houghton, 2007[13] **PCS nested in RCT; Canada** **Summary:** Total synthetic folate intake from supplements and/or fortified foods was associated with plasma folate and RBC folate at 4wk and 16wk postpartum. Synthetic folate intake at 16 weeks postpartum greater than the 2nd quartile (>151–410 µg/d) was not associated with increases in RBC folate levels. **Limitations:**	**Exposure:** Folic acid supplementation during 1-16wk postpartum All women received a daily multivitamin and mineral supplement *Exposure assessment method:* Folate content of supplements was verified analytically. Supplemental folate intakes were determined by assessing the difference between the number of capsules dispensed at randomization (<1wk postpartum) and at 16wk postpartum. In addition, all women agreed not to consume any other folate-containing vitamin or	**Association between Synthetic folate intake (µg) and Plasma folate (nmol/L), Partial correlation** • at 4wk: **r=0.47, P<0.001** • at 16wk: **r=0.49, P<0.0001** **Association between Synthetic folate intake (µg) and RBC folate (nmol/L), Partial correlation** • at 4wk: **r=0.31, P<0.05** • at 16wk: **r=0.36, P<0.01** **Mean RBC folate (nmol/L) at 16wk pp by quartile of synthetic folate intake, ANOVA with Tukey correction** • **Q1 synthetic folate intake (<151 µg/d) < Q3 synthetic folate intake (411-475 µg/d), P<0.05** • Q1 vs Q2 (151-410 µg/d), P=NS • Q1 vs Q4 (>475 µg/d), P=NS

Study	Intervention/Exposure	Outcome and Results
• No information on distribution of missing data or robustness of results despite missing data • No preregistered analysis plan	mineral supplement during the course of the study. Synthetic folate = (µg from supplement) + (µg from fortification) Dietary folate intakes estimated with 3d weighed food records completed over 2 nonconsecutive days and 1 weekend day. Participants were trained by registered dietitians to complete food records using an electronic digital scale accurate to 1 g. Dietary folate intakes tabulated from the diet records using Health Canada's Canadian Nutrient File, based on USDA Nutrient Database for Standard Reference. Dietary folate reported as (1) total dietary folate (sum of naturally occurring folate and folic acid added as fortificant) and (2) folic acid, as a fortificant, separately.	• Q2 vs Q3, P=NS • Q2 vs Q4, P=NS
Uncontrolled Before-and-After Studies		
Tamura, 1980[14] **Uncontrolled Before-and-After; Japan** **Summary:** Consuming folic acid supplements (1mg/d) for 4 weeks in the postpartum period was associated with increased plasma and red blood cell folate levels, but not milk folate levels in lactating mothers. **Limitations:** • Not all key confounders accounted for • No control group; Intervention methods/adherence NR • Statistical analysis NR • Power analysis NR	Maternal intake of 1mg/d synthetic folic acid (PteGlu) for 4 wk, starting 3-25wk postpartum in lactating mothers (N=16).	**Plasma folate (ng/ml), Mean± SD: P=Significant** • Baseline (n=16): 6.0± 2.0 • **Follow-up (n=15): 41.8± 53.8** **RBC folate (ng/ml), Mean± SD: P=Significant** • Baseline (n=16): 250.8± 85.2 • **Follow-up (n=15): 389.9± 85.5**

Table 4. Risk of bias for randomized controlled trials examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and micronutrient status[xii, xiii]

	Randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Blot, 1981[1]	Low	Low	Low	Low	Some Concerns
Caudill, 1997[2]	Some Concerns	Low	Low	Low	Some Concerns
Hekmatdoost, 2015[3]	Low	Low	Low	Low	Some Concerns
Juarez-Vazquez, 2002[4]	Low	Low	Low	Low	Some Concerns
McNulty, 2013[5]	Low	Low	Low	Low	Some Concerns
Shere, 2015[6]	Some Concerns	Low	Low	Low	Some Concerns
Houghton, 2006[10]	Some Concerns	Low	Low	Low	Some Concerns
Keizer, 1995[11]	Low	Low	Some Concerns	Low	Some Concerns
Mackey, 1999[12]	Low	Low	Low	Low	Some Concerns

[xii] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[xiii] Possible ratings of low, some concerns, or high determined using the "Cochrane Risk-of-bias 2.0" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

Table 5. Risk of bias for non-randomized studies of interventions examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and micronutrient status[xiv]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Tamura, 1980[14]	Serious	Low	Moderate	Low	Low	Low	Moderate

Table 6. Risk of bias for observational studies examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and micronutrient status[xv]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Holmes, 2005[7]	Serious	Moderate	Serious	Serious	Low	Low	Moderate
Houghton, 2007[13]	Serious	Low	Low	No Information	Moderate	Low	Moderate
Koebnick, 2001[8]	Serious	Serious	Serious	Moderate	Low	Low	Moderate
Ozer, 2016[9]	Serious	Moderate	Serious	Moderate	Low	Low	Moderate

[xiv] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool" (Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.)

[xv] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

Systematic review question—Gestational diabetes

What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of gestational diabetes?

Conclusion statement and grade

Insufficient evidence is available to determine the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and the risk of gestational diabetes. (Grade: Grade not assignable)

Summary of the evidence

- One NRCT that met the criteria for inclusion in this systematic review was identified through a literature search from 1980 to 2019.[15]
- This study found that women who consumed folic acid supplementation based on genotype and stage of pregnancy had significantly fewer cases of gestational diabetes compared to women who did not consume folic acid supplements before or during pregnancy.
- The evidence had several limitations:
    - No baseline data on study groups were provided for comparison.
    - Intervention methods and adherence were not clear.
    - Results by subgroup were not reported.
    - Consistency could not be assessed with only 1 study.

Description of the evidence

This systematic review included articles that address the relationship between folic acid from supplements and/or fortified foods[ii] consumed before and during pregnancy and the risk of gestational diabetes (**Figure 2**). The search included articles from countries categorized as high or very high on the Human Development Index[iii] and published between January 1980 and June 2019. Studies included generally healthy women up to 6 months before pregnancy and during pregnancy at the time of the intervention or exposure. Study designs that were included were: RCTs, NRCTs, prospective and retrospective cohort studies, nested case-control studies, and uncontrolled before-and-after studies.

One paper met the inclusion criteria for this systematic review (see **Figure 7**). The study was a NRCT that took place in China.[15] Pregnant women were enrolled in the study. They were evaluated for risk of abnormal pregnancy outcomes based on their genotype and polymorphisms of the MTHFR and MTRR genes and classified into levels of risk: “un-identify,” “lower,” “average,” “slightly high,” or “higher.” Based on this classification, women were “guided” to supplement with an individualized dose of folic acid (**Table 7**). A control group consisted of women who did not receive folic acid supplements during the same period of time at the same hospital.

Women were non-smokers and non-drinkers who were mostly between the ages of 20 to 30 years old (71 percent). No other demographic information was provided and therefore, it is not clear if baseline characteristics were similar between groups. Further, no information was provided on intervention methods, adherence, outcome assessment methods, or statistical analyses.

Table 7. Individualized folic acid supplementation plan for women at different levels of risk of abnormal pregnancy outcomes

Risk rank	n	Folic acid (µg/d)		
		3 months before conception	Early pregnancy (0-12 weeks)	Late pregnancy (13-40 weeks)
Un-identify	269	400	400	Dietary
Lower	768	400	400	400
Average	848	400	800	400
Slightly high	587	400	800	400
Higher	446	800	800	400

Evidence synthesis

Women who consumed folic acid supplementation based on genotype and stage of pregnancy had significantly fewer cases of gestational diabetes compared to women who did not consume folic acid supplements before or during pregnancy (0.27 percent and 3.24 percent, respectively; P<0.05) (**Table 8 and Table 9**).

Assessment of the evidence[xvi]

This study had a large enough sample size to detect significant findings; however, there are several limitations to consider. The paper only reports results for all risk levels combined so it is not clear if folic acid supplementation was equally effective across risk levels or preferentially effective for particular subgroups. Further, there was no genetic information from the control group to allow for comparison. No information was provided on exposure methods or adherence. In fact, the supplementation plan, as outlined by risk group (**Table 7**), begins at 3 months prior to pregnancy, yet women were enrolled in the study when they were already pregnant. Therefore, actual duration of intervention is unknown. Little information was reported on baseline characteristics, exposure or outcome methods (**Table 10**).

[xvi] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

Table 8. Description of studies examining the relationship between consumption of folic acid from dietary supplements and/or fortified foods before and during pregnancy and risk of gestational diabetes[xvii, xviii]

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Li, 2015[15] **NRCT; China** **Baseline N=7,812** **Analytic N=7,812 (Attrition: 0%)** **Baseline characteristics:** • Maternal age: <20y: ~3%, 20-30y: ~71%, 30-40y: ~25%, >40y: ~1% • Smoking status: 100% non-smokers • Substance use: 100% non-drinkers • MTHFR status: ○ MTHFR C677T: CC 27.2%, CT 43.7%, TT 29.1% ○ MTHFR A1298C: AA 64.7%, AC 31.0%, CC 4.3% ○ MTRR A66G: AA 54.0%, AG 40.2%, GG 5.8% **Funding Sources:** NR	**Exposure:** Maternal intake of folic acid supplements; folic acid supplement dose varied by genotype and stage of pregnancy; during 3mo before conception (400 or 800 µg/d), 0-12wk gestation (400 or 800 µg/d), 13-40wk gestation (0 or 400 µg/d) 2 groups: • Control: no supplementation (n=4,884) • Intervention: supplementation based on polymorphism (n=2,928) *Exposure assessment method:* NR **Outcome:** • Incidence of gestational diabetes mellitus *Outcome assessment method:* NR	**Confounders accounted for:** • Key confounder: Smoking status (100% non-smokers) • Other factors to be considered: Substance use (100% non-drinkers) **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, SES, Anthropometry, Family history of diabetes or pre-diabetes, Parity • Other factors to be considered: Physical activity, large infant prior, enrolled in intervention/prevention trial, gestational age **Limitations:** • Intervention supposed to have started 3-mo before pregnancy but women recruited while pregnant • Did not report results by intervention subgroup; combined different supplement dosing plans and potentially different supplementation durations into one intervention group • No comparison of baseline characteristics between control and intervention groups; genotypes or risk levels of controls unknown • Statistical analysis methods NR

[xvii] d: day; mo: month(s); MTHFR: methyltetrahydrofolate reductase; NR: not reported; NRCT: Non-randomized controlled trial; SES: socioeconomic status; wk: week(s); y: year(s)
[xviii] Statistically significant findings bolded

Table 9. Results from studies that examined the relationship between folic acid intake from dietary supplements and/or fortified foods before and during pregnancy and risk of gestational diabetes[xix, xx]

Article	Intervention/Exposure	Outcome and Results
Li, 2015[15] **NRCT; China** **Summary:** Women who consumed folic acid supplementation based on genotype and stage of pregnancy had significantly fewer cases of gestational diabetes compared to women who did not consume folic acid supplements before or during pregnancy. **Limitations:** • Intervention supposed to have started 3 mo before pregnancy but women recruited while pregnant • Did not report results by intervention subgroup; combined different supplement dosing plans and potentially different supplementation durations into one intervention group • No comparison of baseline characteristics between control and intervention groups; genotypes or risk levels of controls unknown • Statistical analysis methods NR	Maternal intake of folic acid supplements; folic acid supplement dose varied by genotype and stage of pregnancy; during 3mo before conception (400 or 800 µg/d), 0-12wk gestation (400 or 800 µg/d), 13-40wk gestation (0 or 400 µg/d) 2 groups: • Control: no supplementation (n=4,884) • Intervention: supplementation based on polymorphism (n=2,928)	**Effect of folic acid supplement use on gestational diabetes cases:** Statistical analysis method NR • **Control vs Intervention: 3.24% vs 0.27%, P<0.05**

[xix] d: day; mo: month(s); NR: not reported; NRCT: Non-randomized controlled trial
[xx] Statistically significant findings bolded

Table 10. Risk of bias for the non-randomized controlled trial examining folic acid from dietary supplements and/or fortified foods before and during pregnancy and risk of gestational diabetes[xxi, xxii]

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of the reported result
Li, 2015[15]	**Serious**	**Serious**	**Moderate**	**No Information**	**No Information**	**No Information**	**Moderate**

[xxi] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[xxii] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool" (Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.)

Systematic review question—Hypertensive disorders during pregnancy

What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of hypertensive disorders during pregnancy?

Conclusion statements and grades

Limited evidence suggests that folic acid supplements consumed during early pregnancy may have a beneficial effect on reducing the risk of hypertensive disorders during pregnancy among women at high-risk (e.g., history of preeclampsia or prepregnancy BMI ≥25 kg/m^2) compared to no folic acid supplementation. (Grade: Limited)

Moderate evidence indicates that higher levels of folic acid supplements consumed during pregnancy compared to lower levels (including no folic acid supplementation) does not affect the risk of hypertensive disorders during pregnancy among women at low-risk. (Grade: Moderate)

No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and the risk of hypertensive disorders during pregnancy. (Grade: Grade not assignable)

Summary of the evidence

- Eight studies, including 3 RCTs,[16-18] 2 NRCTs,[15,19] and 3 PCSs,[20-22] met the criteria for inclusion in this systematic review, which were identified through a literature search from 1980 to 2019.
- The 3 RCTs compared 5.0 mg/d of folic acid supplementation to a lower-dose of either 0.5 mg/d (2 studies) or 1.0 mg/d (1 study) from early pregnancy through delivery. The folic acid supplementation dose had no effect on incidence of gestational hypertension, preeclampsia, or eclampsia. None of the studies compared folic acid supplementation to a control group with no folic acid supplementation.
- The 2 NRCTs found a statistically significant association of folic acid supplementation (15 mg/d of 5-MTHF in one study; 400-800 µg/d in another study) from early pregnancy through delivery on risk of gestational hypertension or preeclampsia compared to a control group with no folic acid supplementation. One NRCT was among a high-risk population (women who had preeclampsia in their preceding pregnancy); the other had methodological limitations related to exposure, outcome assessment, and analysis.
- The 3 PCSs reported mixed results. One study found an association between folic acid use in the first trimester and lower incidence of preeclampsia in the full study sample, and specifically among those with a BMI ≥25 kg/m^2; another study found a statistically significant association between folic acid use at 12 to 20 weeks gestation and lower incidence of preeclampsia among high-risk women. A third study did not find a significant association between folic acid supplementation pre and/or post-conception (4 weeks before to 8 weeks after last menstrual period) and preeclampsia. In addition to problems related to confounding, these studies did not account for potential changes in folic acid supplementation during pregnancy.

- No articles were identified that met the inclusion criteria related to folic acid intake from fortified foods and risk of hypertensive disorders during pregnancy.

Description of the evidence

This systematic review included articles that address the relationship between folic acid from supplements and/or fortified foods[ii] consumed before and during pregnancy and the risk of hypertensive disorders during pregnancy (**Figure 3**). The search included articles from countries categorized as high or very high on the Human Development Index[iii] and published between January 1980 and July 2019. Studies included generally healthy women up to 6 months before pregnancy and during pregnancy at the time of the intervention or exposure. Study designs that were included were: RCTs, NRCTs, prospective and retrospective cohort studies, nested case-control studies, and uncontrolled before-and-after studies.

The health outcomes for this systematic review included: gestational hypertension, preeclampsia, and eclampsia; blood pressure (systolic and diastolic) and proteinuria were intermediate outcomes. Outcomes were defined based on The American College of Obstetricians and Gynecologists most recent definitions.[xxiii] *Gestational hypertension* is systolic blood pressure ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg, or both, on two occasions ≥4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure. *Pre-eclampsia* is gestational hypertension with proteinuria or new-onset of other symptoms, including thrombocytopenia (platelet count <100,000/µl), progressive renal insufficiency (>1.1 mg/dl or doubling of serum creatinine in the absence of other renal disease), impaired liver function (twice normal blood concentration of liver transaminases), pulmonary edema, headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms). *Proteinuria* is defined as ≥300 mg/dL of protein in a 24-hour urine collection or a protein-to-creatinine ratio of ≥0.30. If urinalysis is the only means of assessment, a dipstick of 2+ can also be used to identify proteinuria. *Eclampsia* is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use.

This body of evidence included 8 studies (3 RCTs,[16-18] 2 NRCTs,[15,19] and 3 prospective cohort studies (PCS)[20-22]) (see **Table 11** and **Table 12** for study characteristics and results; see **Figure 7** for search results). The RCTs took place in Iran; the NRCTs were conducted in Italy[19] and China[15]; and the PCSs were from Canada (Ottawa and Kingston (Oak) birth cohort),[22] Australia (Environments for Healthy Living (EFHL) cohort),[21] and Denmark (Danish Birth Cohort).[20]

Participant characteristics

Across the body of evidence, women were mostly between the age of 20 and 40 years. The RCTs had a mean age of approximately 25 years. Women in the RCTs were living in Iran and had a mean BMI of approximately 25 kg/m^2. Race/ethnicity was either not reported (studies from Iran,[16-18] China,[15] and Denmark[20]) or tended to have a majority of Caucasians.[19,21,22] One NRCT specifically recruited women who had preeclampsia in an immediately preceding pregnancy.[19] Racially and ethnically diverse

[xxiii] ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019;133(1):e1. doi:10.1097/AOG.0000000000003018

populations were underrepresented in the PCSs, which were conducted in Denmark,[20] Australia,[21] and Canada.[22] The sample sizes of the PCSs allowed authors to examine the association between folic acid supplementation and hypertensive disorders among both high and low risk groups, as detailed in the Evidence Synthesis.

Interventions/Exposures

Dose and composition

The controlled trials (both the RCTs and NRCTs) provided an intervention that lasted from early pregnancy through delivery. Each of the 3 RCTs had 2 intervention arms: a low dose folic acid supplement (either 0.5 mg/d or 1.0 mg/d) and a high dose folic acid supplement (5.0 mg/d). In the double blind RCT by Shahraki et al,[18] women were given either 1.0 mg/d or 5.0 mg/d folic acid and asked not to use multivitamins during pregnancy. In the other 2 RCTs conducted by the same group, women were given either 0.5mg/d or 5.0mg/d folic acid; in addition, all women were given 1 g/d calcium and 60 mg/d ferrous sulfate from 14 weeks gestation to delivery.[16,17] In 1 NRCT, women elected to take 15 mg/d 5-MTHF supplements daily plus aspirin (intervention group) or declined the 5-MTHF supplementation and took aspirin daily (control group).[19] In the other NRCT, women were guided to take daily folic acid supplements based on a dose individualized according to genotype and stage of pregnancy (folic acid dose was either 400 mg/d or 800 mg/d, varying by time point: 3 months before pregnancy, early pregnancy, and late pregnancy), without reference to the use of other supplements during pregnancy.[15]

Timing of exposure

One key difference in the PCS compared to the controlled trials is the timing of folic acid exposure. While the trial interventions lasted from early pregnancy up to delivery,[15-19] the cohort studies looked for associations between folic acid supplementation in early pregnancy with hypertensive disorders later in pregnancy, without accounting for changes in folic acid use during pregnancy.[20-22] Exposure data was assessed at one point in time by self-report in the cohort studies.

Outcome

A primary outcome for most studies was preeclampsia, but RCTs also reported other outcomes including: eclampsia, gestational hypertension, blood pressure, and proteinuria. The outcome definitions from the papers were similar to the ACOG definitions. The most common difference in definitions was related to gestational hypertension and preeclampsia. Some papers either did not report a time requirement between blood pressure measurements (i.e. blood pressure readings “on 2 occasions ≥4 hours apart” (ACOG)) or used “≥6 hours apart” instead of “≥4 hours apart.”

Evidence synthesis

Eight studies examining the relationship between folic acid intake from supplements and risk of hypertensive disorders during pregnancy were included in the review. Three of these studies were RCTs,[16-18] 2 were NRCTs,[15,19] and 3 were prospective cohort studies.[20-22] Results varied across the body of evidence. The RCTs[16-18] reported no statistically significant effect of high doses compared to low doses of folic acid supplement (5.0 mg/d vs 0.5 mg/d or 1.0 mg/d, respectively) on eclampsia, preeclampsia, gestational hypertension, blood pressure (systolic and diastolic), and proteinuria. The 2 NRCTs reported statistically significant protective effects of folic acid

supplementation compared to no supplementation on gestational hypertension and preeclampsia.[15,19] The prospective cohort studies had mixed findings (See **Table 12**).[20-22]

Three RCTs, which all took place in generally healthy women in Iran, reported no difference in hypertensive disorders during pregnancy between low dose and high dose folic acid supplementation.[16-18] Two of these studies were from the same research center and had very similar designs and sample populations (N=460[17] and N=246[16]). They compared 0.5 mg/d to 5.0 mg/d of folic acid and found no effect of folic acid dose on blood pressure. Across both studies, only 1 case of gestational hypertension was identified; no cases of preeclampsia or eclampsia were identified. The third study, also in generally healthy women from Iran but from a different research center, compared 1.0 mg/d to 5.0 mg/d of folic acid.[18] This study had a larger sample size (N=900) compared to the other RCTs and more cases of preeclampsia (17 cases in the low folic acid group, 11 cases in the high folic acid group); yet there were no significant differences in prevalence, severity, or time of onset of preeclampsia between the groups.

In contrast, 2 NRCTs found a statistically significant effect of folic acid supplementation on gestational hypertension[15] and preeclampsia.[19] In a trial by Saccone et al[19] women who had preeclampsia in a previous pregnancy and elected to take 15 mg/d of 5-MTHF supplements and aspirin during pregnancy had a lower incidence of preeclampsia compared to those who only took aspirin (21.7 percent and 39.7 percent, respectively). Further, in a subgroup analysis in women without other medical conditions, those who were supplemented with 5-MTHF had lower incidence of preeclampsia, severe preeclampsia, and early onset preeclampsia compared to women who did not take 5-MTHF supplements. Li[15] reported that women with an individualized folic acid supplementation plan presented with fewer cases of gestational hypertension than women who did not take folic acid supplements throughout pregnancy.

Results were mixed from the 3 prospective cohort studies that examined the association between folic acid supplementation in early pregnancy and incidence of preeclampsia. Unlike the trials, the exposure period for these studies was only assessed in early pregnancy with no indication of supplementation changes throughout pregnancy. Vanderlelie et al[21] found that folic acid supplement use in the first trimester was associated with a lower incidence of preeclampsia compared to no supplement use (1.26 percent and 2.9 percent, respectively). This was true for the full study population and specifically in women with BMI ≥25 kg/m^2, but not among women with BMI <25 kg/m^2. While Wen et al[22] did not find a statistically significant association between folic acid use in early pregnancy and risk of preeclampsia for the study sample, folic acid use was associated with reduced risk of preeclampsia in a subgroup of high-risk women. High-risk was defined as a prepregnancy BMI ≥35 kg/m^2, preeclampsia in a previous pregnancy, chronic hypertension, diabetes, or multiple pregnancy. Finally, Catov[20] did not find a statistically significant association between folic acid supplementation during pre- and post-conception (from 4 weeks before the last menstrual period to 8 weeks after the last menstrual period) or post-conception only (3 to 8 weeks after last menstrual period) on risk of preeclampsia.

There are substantial differences among the studies and important limitations to

consider. First, the 3 RCTs are controlled studies in which the intervention began in early pregnancy and continued through delivery. Each RCT compared a lower to higher dose folic acid supplementation, but unlike the rest of the evidence, they did not include a control group with no folic acid supplementation. Participants were generally healthy and likely at low-risk for hypertensive disorders of pregnancy. Further, some participant characteristics were not reported or accounted for.

The non-randomized trials also started in early pregnancy and continued through delivery. However, the sample in the Saccone et al[19] study was comprised only of high-risk women (women who had preeclampsia in the preceding pregnancy) and a higher dose than the other NRCTs (15 mg/d 5-MTHF). The Li et al[15] study lacked explanation of intervention, outcome, and analysis methods. One other concern worth noting is that Li et al[15] indicated that the individualized supplementation plan began 3 months prior to pregnancy, yet, women were recruited after the start of pregnancy. Further, in both NRCTs certain key confounders were not accounted for and could have differed between groups. While Saccone et al[19] accounted for several confounders, the authors note that refusal to participate in the intervention was likely due to economic reasons; the only confounder that Li et al[15] accounted for was smoking status.

In the 3 prospective cohort studies folic acid supplement use during early pregnancy was the exposure, but time of assessment varied. Wen et al[22] noted that folic acid use was assessed any time between 12 and 20 weeks gestation possibly resulting in different time to follow-up across the participants. Vanderlelie et al[21] recruited women at any point during pregnancy and asked about supplementation during the first trimester, introducing potential for recall bias. Catov et al[20] on the other hand, obtained more detailed information on supplement use from pre-conception to post-conception. These studies did not account for potential changes in supplement use during pregnancy or differences in doses that could have impacted the results. Further, all exposure data was based on self-report.

Publication bias is always a consideration, however it is not a serious concern for this body of evidence because half of the studies reported only non-significant findings while the other half report significant findings or a mix of significant and non-significant.

Assessment of the evidence[xxiv]

The conclusion statement "evidence suggests that folic acid supplements consumed during early pregnancy may have a beneficial effect on reducing the risk of hypertensive disorders during pregnancy among women at high-risk (e.g. history of preeclampsia or pre-pregnancy BMI ≥25 kg/m^2) compared to no folic acid supplementation" was assigned a grade of **limited**. This conclusion statement is supported by the 2 NRCTs and the 3 prospective cohort studies, and no RCT data. As outlined and described below, the body of evidence examining folic acid supplementation during early pregnancy and risk of hypertensive disorders during pregnancy was assessed for the following elements used when grading the strength of evidence (**Table 14**):

- **Risk of Bias**: The 2 NRCTs were graded as limited due to serious concerns about the design and conduct of the studies. For example, in the study by Saccone et al[19] the authors speculated that many women chose to be in the control group rather than the intervention group due to economic reasons, yet socioeconomic status was not accounted for in the analysis. The study by Li et al[15] lacked information on intervention methods and outcome assessment, and had missing data. There were fewer concerns related to the 3 prospective cohort studies. These papers controlled for all or all but 1 key confounder. The main risk of bias concerns across these studies were classification of exposures and deviation from the intended exposure. Exposures were based on self-reported data representing folic acid supplementation before or during early pregnancy. Little information was provided on dose or duration of supplement use, and no follow-up exposure assessment was reported to indicate whether women adhered to the same folic acid supplementation throughout pregnancy prior to outcome assessment.
- **Consistency**: Considering that this conclusion statement is specific to women at high risk for hypertensive disorders during pregnancy, consistency was moderate. In studies or analyses specific to high risk women, results showed a protective association between folic acid supplementation and incidence of preeclampsia.
- **Directness**: The studies supporting this conclusion statement were direct, such that they represent the population, exposure, comparator, and outcome intended by the systematic review.
- **Precision**: Precision was limited due to the small sample sizes and number of cases, differences in prevalence across studies, and wide confidence intervals.
- **Generalizability**: These studies were limited in generalizability. None of the studies were conducted in the United States. There was little racial/ethnic diversity and little data provided on other participant characteristics.

[xxiv] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

The conclusion statement “evidence suggests that higher levels of folic acid supplements consumed during pregnancy compared to lower levels (including no folic acid supplementation) may not have an effect on the risk of hypertensive disorders during pregnancy among women at low-risk” was assigned a grade of **moderate**. This conclusion was supported by the 3 RCTs and 3 prospective cohort studies. As outlined and described below, the body of evidence examining folic acid supplementation during pregnancy and hypertensive disorders during pregnancy was assessed for the following elements used when grading the strength of evidence (**Table 13 and Table 15**):

- **Risk of Bias**: Across the RCTs and PCSs, there was moderate risk of bias. Some of the concerns include: 1) randomization method for 1 RCT,[16] 2) missing data in another RCT,[17] which may be problematic due to the low number of cases, and 3) none of the RCTs having preregistered protocols with a priori analysis plans. As noted above, the PCSs controlled for all or all but 1 key confounder but had other risk of bias concerns. The main risk of bias concerns across these studies were classification of exposures and deviation from the intended exposure. Exposures were based on self-reported data representing folic acid supplementation before or during early pregnancy. Little information was provided on dose or duration of supplement use, and there was no follow-up exposure assessment to indicate whether women adhered to the same folic acid supplementation throughout pregnancy prior to outcome assessment.
- **Consistency**: Consistency was strong, such that for all studies or analyses in low risk populations (including all 3 RCTs) there was no significant association between higher versus lower levels of folic acid supplementation and risk of hypertensive disorders.
- **Directness**: The studies supporting this conclusion statement were direct, such that they represent the population, exposure, comparator, and outcome intended by the systematic review.
- **Precision**: Precision for this evidence was moderate due to small sample sizes and number of cases, and concerns that studies were not sufficiently powered.
- **Generalizability**: Again, no studies were conducted in the United States. The 3 RCTs took place in relatively healthy populations in Iran. The PCSs were conducted in Australia, Canada and Denmark and had little racial/ethnic diversity and little data on other participant characteristics. Thus, the rating was limited.

Further, no evidence is available to draw a conclusion about the relationship between folic acid from fortified foods consumed before and during pregnancy and the risk of hypertensive disorders during pregnancy. (Grade not assignable)

Table 11. Description of studies examining the relationship between consumption of folic acid from dietary supplements and/or fortified foods during pregnancy and risk of hypertensive disorders during pregnancy[xxv,xxvi]

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Randomized Controlled Trials		
Manizheh, 2009[16] **RCT; Iran (Islamic Rep. of)** **Baseline N=246** **Analytic N=200 (Attrition: 19%)** **Power calculation:** Recruit N=230/group for serum Hcy **Baseline characteristics:** • Maternal age: 24.7±3.2y • Prepregnancy BMI: ~24.9±3.0 • History/diagnosis (HTN or CVD): chronic disease excluded • Parity: 100% nulliparous **Funding Sources:** The Drug Research Center	**Exposure:** Maternal intake folic acid supplements <10wk gestation to delivery; 2 groups: • 0.5 mg/d (Ref, n=123) • 5.0 mg/d (n=123) All received 1 g/d calcium + 60 mg/d ferrous sulfate from 16wk gestation to delivery *Exposure assessment method:* Single blind, randomized trial of folic acid. From 16wk gestation, 1 g/d calcium plus 60 mg/d ferrous sulfate were administered to participants. **Outcome:** • Preeclampsia, Blood pressure (systolic and diastolic) at delivery *Outcome assessment method:* Systolic and diastolic BP. Severe PE: BP ≥160/10mm Hg, proteinuria ≥2.0 g/24 hrs, or ≥2+ dipstick, serum creatine > 1.2 mg/dl unless known to be previously elevated, platelets <100000 mm^3, microangiopathic hemolysis, elevated alanine aminotransferase, or aspartate aminotransferase, persistent	**Confounders accounted for:** • Maternal age, Anthropometry, History of HTN or CVD, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES, Smoking status • Other factors considered: PA, Substance use, Gestational age, GDM diagnosis **Limitations:** • Randomization and allocation method NR • No preregistered protocol with analysis plan • Unclear statistical methods

[xxv] Values indicate mean± standard deviation unless otherwise stated

[xxvi] BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; d: day; DNBC: Danish National Birth Cohort; EFHL: Environments for Healthy Living cohort; FA: folic acid; GA: gestational age; GDM: gestational diabetes; GH: gestational hypertension; Hcy: homocysteine; HTN: hypertension; mo: month(s); MTHF: methyltetrahydrofolate; NR: not reported; NRCT: non-randomized controlled trial; OaK: Ottawa and Kingston Birth Cohort; PA: physical activity; PE: pre-eclampsia; RCT: randomized controlled trial; SES: socioeconomic status; wk: week(s); y: year(s)

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
	headache or other cerebral, or visual disturbance and persistent epigastric pain.	
Sayyah-Melli, 2016[17] **RCT; Iran (Islamic Rep. of)** **Baseline N=460** **Analytic N=410 (Attrition: 11%)** **Power calculation:** N=230/group (based on serum Hcy) **Baseline characteristics:** • Maternal age: 0.5mg/d FA: 25.2±3.4y, 5.0mg/d FA: 25.2±3.8y; P=0.93 • Prepregnancy BMI: 0.5mg/d FA: 25.1±3.4, 5.0mg/d FA: 24.7±2.9, P=0.21 • GDM: 100% "healthy mothers" without "any history of medical problems" • History/diagnosis (HTN or CVD): 0% heart disease or chronic HTN • Parity: 100% nulliparous **Funding Sources:** Drug Applied Research Center, Tabriz University of Medical Sciences	**Exposure:** Maternal intake of folic acid from supplements from early pregnancy until delivery; 2 groups: • 0.5 mg/d FA (Ref, n=230) • 5.0 mg/d FA (n=230) All received 1 g/d calcium + 60 mg/d ferrous sulfate from 14wk gestation to delivery *Exposure assessment method:* All participants received 1 g calcium and 60 mg ferrous sulfate from 14wk gestation through delivery, and either 0.5 or 5.0 mg folic acid/d from early pregnancy to delivery **Outcome:** • Eclampsia, Preeclampsia, Gestational hypertension, Proteinuria, Blood pressure (systolic and diastolic) *Outcome assessment method:* Blood pressure was measured monthly from randomization until 28wk gestation, every 2wk from 28-36wk gestation, and weekly from 36wk until delivery. Urine protein was measured at the first visit and delivery. *Standard outcome definitions with the following differences:* GH and PE: blood pressure measured ≥6h, rather than ≥4h apart; Severe PE: standard definition with proteinura or other new-onset symptoms.	**Confounders accounted for:** • Maternal age, Anthropometry, History of HTN or CVD, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES, Smoking status • Other factors considered: PA, Substance use, Gestational age, GDM diagnosis **Limitations:** • Participants and researchers not blinded • Some missing data could be problem due to low number of cases reported • No preregistered protocol with analysis plan; not clear that all outcome data and analyses reported (did not report results for proteinuria)
Shahraki, 2016[18] **RCT; Iran (Islamic Rep. of)** **Baseline N=900** **Analytic N=900 (Attrition: 0%)**	**Exposure:** Maternal intake of folic acid supplements from first trimester until delivery; 2 groups: • 1mg/d FA (Ref, n=450) • 5mg/d FA (n=450)	**Confounders accounted for:** • Maternal age, Anthropometry, History of HTN, Parity **Not accounted for:** • Key confounders: Race/ethnicity, SES, Smoking status • Other factors considered: PA, GDM diagnosis

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Baseline characteristics: • Maternal age: 28.1±5.3y • Prepregnancy BMI: 25±3.52 • History/diagnosis (HTN or CVD): History of PE (N): 5mg FA: 23, 1mg FA: 32; P>0.05 • Gravidity: 1.96±1.0 • Substance use: 0% alcohol "abuse" • GA: 100% first trimester at enrollment **Funding Sources:** Isfahan University of Medical Sciences	*Exposure assessment method:* Double-blind design; participants followed up monthly in the first and second trimesters to collect old and provide new pillboxes, then every 2wk until 36wk, then weekly till delivery. Participants asked to not to use multivitamins during the study. **Outcome:** • Preeclampsia, Proteinuria, Blood pressure (systolic and diastolic) *Outcome assessment method:* Blood pressure (systolic and diastolic) measured every 2wk from 20-36wk gestation then weekly until delivery. *Standard outcome definitions with the following differences:* no reassessment of BP ≥4h apart.	**Limitations:** • Some participant characteristics unknown, may differ between groups, not accounted for in analysis (SES, smoking, physical activity) • No preregistered protocol with analysis plan • Power calculation NR
Non- Randomized Controlled Trials		
Li, 2015[15] **NRCT; China** **Baseline N=7812** **Analytic N=7812 (Attrition: 0%)** **Baseline characteristics:** • Maternal age: <20y ~3%, 20-30y ~71%, 30-40y ~25%, >40y ~1% **Funding Sources:** NR	**Exposure:** Maternal intake of folic acid supplements during 3mo before conception, early pregnancy (0-12wk gestation) and/or late pregnancy (13-40wk gestation); 2 groups: • No (Ref, n=4884) • Yes (n=2928) *Exposure assessment method:* NR **Outcome:** • Gestational hypertension *Outcome assessment method:* NR	**Confounders accounted for:** • Smoking status **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, SES, Anthropometry, History of HTN or CVD, Parity • Other factors considered: PA, Gestational age, GDM diagnosis **Limitations:** • Intervention supposed to have started 3-mo before pregnancy but women recruited while pregnant • Did not report results by intervention subgroup; combined different supplement dosing plans and potentially different supplementation durations into one intervention group • No comparison of baseline characteristics between control and intervention groups; genotypes or risk levels of controls unknown • Statistical analysis methods NR • Power calculation NR

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Saccone, 2016[19] **NRCT; Italy** **Baseline N=303** **Analytic N=303 (Attrition: 0%)** **Baseline characteristics:** • Maternal age: ~31±6.0y • Race/Ethnicity: Caucasian: 100% • SES: Control group declined 5-MTHF mostly for economic reasons • Prepregnancy BMI: ~27±6.2y • Smoking status: 16% • History/diagnosis (HTN or CVD): 0% chronic HTN; 0% prior GH without PE; Family history of HTN: 37% • Parity: Gravidity: 2.2, GA: Prior delivery: 35±3.6wk • MTHFR status: 0% MTHFR mutations • All women had PE in immediately previous pregnancy **Funding Sources:** No financial support received for this study	**Exposure:** Maternal intake of 15 mg/d 5-MTHF supplementation; from <14 wk gestation through delivery; 2 groups: • Control: aspirin alone (Ref, n=146) • Intervention:15 mg/d 5-MTHF + aspirin (n=157) *Exposure assessment method:* Women with singleton pregnancy and diagnosis of preeclampsia in the immediately previous pregnancy were offered and declined (Controls, n=146) or accepted (Intervention, n=157) supplementation with 15 mg/d 5-MTHF from first trimester assessment (<14 wk gestation) through delivery. All women included in the study received 100 mg/d aspirin. **Outcome:** • Preeclampsia *Outcome assessment method:* *Standard outcome definitions with the following differences:* includes BP ≥160/110 mmHg once; severe PE: PE with either: BP ≥160/110 mmHg, ≥4h apart on bed rest (unless on anti-hypertensive) OR other new-onset symptoms	**Confounders accounted for:** • Maternal age, Race/ethnicity, Anthropometry, Smoking status, History of HTN or CVD, Parity **Not accounted for:** • Key confounders: SES • Other factors considered: PA, Substance use, Gestational age, GDM diagnosis **Limitations:** • Control group declined 5-MTHF mostly for economic reasons • No preregistered protocol with analysis plan; results reported for multiple subgroups • Power calculation NR
Cohort Studies		
Catov, 2009[20] **PCS (DNBC); Denmark** **Baseline N=10050** **Analytic N=10050 (Attrition: 0%)** **Baseline characteristics:**	**Exposure:** Maternal intake of folic acid supplements during periconceptional period (4 wk before LMP – 8 wk after LMP); 2 groups: • Non-users (Ref, n=7582) • FA-only users (n=2468) *Exposure assessment method:*	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking status, History of HTN or CVD, Parity **Not accounted for:** • Other factors considered: GDM diagnosis **Limitations:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Maternal age: <21y: 2.1%, 21–25y: 15.5%, 26–30y: 40.7%, 31–35y: 30.3%, ≥36y: 11.4% • Race/Ethnicity: Maternal country of origin: Denmark or other Nordic countries: 96.2%, Greenland and Faroe Islands: 0.8%, Other: 2.9% • SES: Low sociooccupational status (unskilled, unemployed): 6.1% • Prepregnancy BMI: <18.5: 4.3%, 18.5–24.9: 63.8%, 25–29.9: 21.3%, ≥30: 10.6% • Smoking status: 1–10 cigarettes/d: 14.3%, >10 cigarettes/d: 5.0% • History/diagnosis (HTN or CVD): Chronic hypertension: 1.5% • Parity: Multiparous: 53.6% • PA: 0 min/wk: 66.2%, 1-180 min/wk: 26.4% • Substance use: 0 drinks/wk: 56.1%, 0.5–3 drinks/wk: 41.3%, >3 drinks/wk: 2.5% • GA: At recruitment: ~11±3.6wk **Funding Sources:** Danish National Research Foundation; the Pharmacy Foundation; the Egmont Foundation; the March of Dimes Birth Defects Foundation; the Augustinus Foundation, the Health Foundation; the BIRCWH	At recruitment (10.8±3.6wk, range 5-24wk), women completed a table indicating weekly supplement type and frequency from 4wk before last menstrual period (LMP) through 14wk after the LMP. **Outcome:** • Preeclampsia *Outcome assessment method:* *Standard outcome definitions with the following differences:* no requirement of 2 blood pressure measures ≥4h apart, no option of diagnosis with other new-onset symptoms; PE categorized into those delivered at term (≥37 wk) or preterm (<37 wk).	• Exposure based on self-report at recruitment • Participants may have changed supplementation during pregnancy • No preregistered protocol with analysis plan
Vanderlelie, 2016[21] **PCS (EFHL); Australia** **Baseline N=2619** **Analytic N=2261 (Attrition: 14%)** **Baseline characteristics:**	**Exposure:** Maternal intake of folic acid supplements during first trimester; 2 groups: • No supplement (Ref, n=1066) • Folate only (n=476) *Exposure assessment method:*	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking status, Parity, GDM diagnosis **Not accounted for:** • Key confounders: History of HTN or CVD • Other factors considered: PA, Substance use, Gestational age

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Maternal age: ○ <18y: ~1% ○ 18-21y: ~11% ○ 22-24y: ~15% ○ 25-29y: ~30% ○ 30-34y: 25% ○ ≥35y: ~19% • Race/Ethnicity: Aboriginal and Torres Strait Islander descent: ~2% • SES: Household income quintile: ○ 1: ~17% ○ 2: ~17% ○ 3: ~18% ○ 4: ~16% ○ 5: ~15% ○ Declined to answer: ~16% • Prepregnancy BMI: ○ <18.5: ~8% ○ 18.5-24.9: ~51% ○ 25-29.9: ~20% ○ 30-34.9: ~12% ○ ≥35: ~7% • Smoking status: Smoker: ~25% • Parity: ○ Nulliparous: ~27% ○ Multiparous: ~73% **Funding Sources:** Griffith University	Self-reported questionnaire at baseline to assess maternal characteristics, including supplement use. Data were obtained for multivitamin/mineral preparations, folate, zinc, calcium, vitamin C, vitamin E, iron and other supplements with individual questions for each supplement related to supplement use in the periconception period, first, second and third trimesters of pregnancy. Women also had the opportunity to name the preparation, which in a number of cases was a multivitamin/mineral supplement. For these cases, use of the 'other supplement' was considered a multivitamin/mineral and included in the analysis. **Outcome:** • Preeclampsia *Outcome assessment method:* Diagnosed in hospital; *Standard outcome definitions with the following differences:* BP >140/90 mmHg or a rise of >30 mmHg or >15 mmHg above initial systolic and diastolic pressures, respectively, and proteinuria	**Limitations:** • Not all key confounders accounted for • Dose, duration of FA supplementation unknown • Self-report of supplementation from different stages of pregnancy (some retrospectively); Participants may have changed supplementation during pregnancy • Study registered but no preregistered analysis plan
Wen, 2016[22] **PCS (OaK); Canada** **Baseline N=8085** **Analytic N=7669 (Attrition: 5%)** **Baseline characteristics:** • Maternal age: • <20y: n=2.3%	**Exposure:** Maternal intake of folic acid supplements; at 12-20wk gestation; 2 groups: • No supplement (Ref, n=404) • FA alone (n=625) *Exposure assessment method:*	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking status, History of HTN or CVD, Parity **Not accounted for:** • Other factors considered: PA, Substance use, GDM diagnosis **Limitations:** • Exposure based on self-report at enrollment which varied

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• 20-29y: (39.6%) • 30-34y: 37.0%, ≥35y: 21.1% • Race/Ethnicity: ○ Aboriginal: 0.49% ○ White: 74.6% ○ Middle Eastern: 2.4% ○ Africa: 1.2% ○ Asian: 4.7% ○ Other: 16.6% • SES: Education: ○ High school and below: 14.6% ○ College/university not completed: 9.9% ○ College/university completed: 75.4% • Household income ($CAD): <25000: 5.4%, 25,000–49,999: 15.5%, 50,000–79,999: 27.3%, ≥80,000: 4.5% • Prepregnancy BMI: <18.5: 5.5%, 18.5–24: 56.8%, 25–29: 22.7%, ≥30: 9.2%, ≥35: 5.8% • Smoking status: Smokers: 11.4% • History/diagnosis (HTN or CVD): Chronic Hypertension: 1.2% • Parity: Parity ≥1: 49.8% • Substance use: Alcohol use: 0.8% • GA: At recruitment: ≤12wk: 58.1%, 13–15wk: 27.0%, 16–20wk: 14.9% **Funding Sources:** Canadian Institutes of Health Research	Maternal self-report of folic acid supplementation at recruitment (12-20wk gestation) and at delivery (delivery data NR). **Outcome:** • Preeclampsia *Outcome assessment method:* *Standard outcome definitions with the following differences:* blood pressure measures ≥6h apart rather than ≥4h apart	between 8 – 20 GW • Dose, duration of FA supplementation unknown; Participants may have changed supplementation during pregnancy • Few participants consumed no supplements or folic acid alone resulting in low power • No preregistered protocol with analysis plan

Table 12. Results from studies that examined the relationship between folic acid intake from dietary supplements and/or fortified foods during pregnancy and risk of hypertensive disorders of pregnancy[xxvii, xxviii]

Article	Intervention/Exposure	Outcome and Results
Randomized Controlled Trials		
Manizheh, 2009[16] **RCT; Iran (Islamic Rep. of)** **Summary:** Consuming 0.5 or 5.0 mg/d folic acid from first trimester of pregnancy to delivery was not associated with maternal blood pressure at delivery. **Limitations:** • Randomization and allocation method NR • No preregistered protocol with analysis plan • Unclear statistical methods	Maternal intake folic acid supplements <10wk gestation to delivery; 2 groups: • 0.5 mg/d (Ref, n=123) • 5.0 mg/d (n=123) All received 1 g/d calcium + 60 mg/d ferrous sulfate from 16wk gestation to delivery	**Any pregnancy-induced hypertension** • 0.5 mg/d FA: n=0 • 5.0 mg/d FA: n=0 **Systolic BP (mmHg, Mean±SD)**, P=0.32 (comparison not clear) • 0.5 mg/d FA: ○ @ First trimester: 117.24±6.91 ○ @ Delivery: 117.23±11.48 • 5.0 mg/d FA: ○ @ First trimester: 114.01±8.78 ○ @ Delivery: 114.16±9.05 **Diastolic BP (mmHg, Mean±SD)**, P=0.42 (comparison not clear) • 0.5 mg/d FA: ○ @ First trimester: 76.46±5.58 ○ @ Delivery: 76.69±8.62 • 5.0 mg/d FA: ○ @ First trimester: 74.90±7.45 ○ @ Delivery: 73.30±8.90 **24hr urine protein (mg, Mean±SD)**, P=<0.001 (comparison not clear) • 0.5 mg/d FA: ○ @ First trimester: 33.96±36.55 ○ @ Delivery: 105.85±109.10 • 5.0 mg/d FA: ○ @ First trimester: 25.90±33.10

[xxvii] AOR: adjusted odds ratio; BMI: body mass index; BP: blood pressure; d: day; DNBC: Danish National Birth Cohort; EFHL: Environments for Healthy Living cohort; FA: folic acid; LMP: last menstrual period; mo: month(s); MTHF: methyltetrahydrofolate; NR: not reported; NRCT: non-randomized controlled trial; NS: Non-significant; OaK: Ottawa and Kingston Birth Cohort; PE: pre-eclampsia; RCT: randomized controlled trial; SD: standard deviation; SES: socioeconomic status; wk: week(s)

[xxviii] Statistically significant findings bolded

Article	Intervention/Exposure	Outcome and Results
		○ @ Delivery: 44.29±66.14
Sayyah-Melli, 2016[17] **RCT; Iran (Islamic Rep. of)** **Summary:** Consuming 5.0 mg/d vs 0.5 mg/d folic acid supplements throughout pregnancy was not associated with differences in blood pressure, risk of gestational hypertension, pre-eclampsia or eclampsia. **Limitations:** • Participants and researchers not blinded • Some missing data could be problem due to low number of cases reported • No preregistered protocol with analysis plan; not clear that all outcome data and analyses reported (did not report results for proteinuria)	Maternal intake of folic acid from supplements from early pregnancy until delivery; 2 groups: • 0.5 mg/d FA (n=230) • 5.0 mg/d FA (n=230) All received 1 g/d calcium + 60 mg/d ferrous sulfate from 14wk gestation to delivery	**Eclampsia**, P=NR • 0.5mg/d FA: n=0 (0%) • 5.0mg/d FA: n=0 (0%) **Pre-eclampsia**, P=NR • 0.5mg/d FA: n=0 (0%) • 5.0mg/d FA: n=0 (0%) **Gestational hypertension**, P=NR • 0.5mg/d FA: n=1 (0.9%) • 5.0mg/d FA: n=0 (0%) **Systolic BP (Mean±SD mmHg)**, Independent T-test; NS, P>0.05 • 0.5mg/d FA: ○ Baseline: 118.92±8.11 ○ Endpoint: 120.59±10.61 • 5.0mg/d FA: ○ Baseline: 116.31±9.52 ○ Endpoint: 117.36±9.51 **Diastolic BP (Mean±SD)**, Independent T-test; NS, P>0.05 • 0.5mg/d FA: ○ Baseline: 76.50±5.87 ○ Endpoint: 78.07±7.18 • 5.0mg/d FA: ○ Baseline: 74.57±7.53 ○ Endpoint: 74.73±7.44
Shahraki, 2016[18] **RCT; Iran (Islamic Rep. of)** **Summary:** Consuming 5mg vs 1mg folic acid supplements throughout pregnancy was not associated with reduced prevalence of pre-eclampsia and did not alter the severity or onset of pre-eclampsia.	Maternal intake of folic acid supplements from first trimester until delivery; 2 groups: • 1mg/d FA (Ref, n=450) • 5mg/d FA (n=450)	**PE prevalence**: Independent t-test, P >0.05 • 1 mg FA: n=17 (3.8%) • 5 mg FA: n=11 (2.4%) **Severity of PE**: Fisher's test, P=0.2 • 1 mg FA: Non severe PE: n=15 (88.2%), Severe PE: n=2 (11.8%) • 5 mg FA: Non severe PE: n=11 (100%), Severe PE: n=0 (0%) **Onset of PE**: Fisher's test, P=0.06

Article	Intervention/Exposure	Outcome and Results
Limitations: • Some participant characteristics unknown, may differ between groups, not accounted for in analysis (SES, smoking, physical activity) • Power calculation NR		• 1 mg FA: <34wk: n=9 (52.9%), ≥34wk: n=8 (47.1%) • 5 mg FA: <34wk: n=2 (18.2%), ≥34wk: n=9 (81.8%) **BP among PE patients**, Fisher's test, P=0.6 • 1 mg FA: ○ ≥140/90 mmHg: n=16 (94.1%) ○ ≥160/110 mmHg: n=1 (5.9%) • 5 mg FA: ○ ≥140/90 mmHg: n=11 (100%) ○ ≥160/110 mmHg: n=0 (0%) **24h urinary protein among PE patients**, Fisher's test, P=0.4 • 1 mg FA: ○ ≥300 mg: n=16 (94.1%) ○ ≥500 mg: n=1 (5.9%) • 5 mg FA: ○ ≥300 mg: n=11 (100%) ○ ≥500 mg: n=0 (0%) **Protein urine dipstick among PE patients**, Fisher's test, P=0.7 • 1 mg FA: ○ ≤1: n=1 (5.9%) ○ ≥2: n=16 (94.1%) • 5 mg FA: ○ ≤1: n=1 (9.1%) ○ ≥2: n=10 (90.9%)
Non-Randomized Controlled Trials		
Li, 2015[15] **NRCT; China** **Summary:** Women who consumed folic acid supplementation during 3mo (400 or 800 µg/d) before conception, early pregnancy (0-12wk gestation, 400 or 800 µg/d) and/or late pregnancy (13-40wk gestation, 0 or 400 µg/d) had significantly lower cases of gestational hypertension	Maternal intake of folic acid supplements during 3mo before conception, early pregnancy (0-12wk gestation) and/or late pregnancy (13-40wk gestation); 2 groups: • No (Ref, n=4884) • Yes (n=2928)	**Gestational hypertension**, Analysis NR, **P<0.05** • Control: n=48 (0.98%) • Intervention: n=1 (~0%)

Article	Intervention/Exposure	Outcome and Results
compared to women who did not consume folic acid supplements. **Limitations:** • Intervention supposed to have started 3mo before pregnancy but women recruited while pregnant • Did not report results by intervention subgroup; combined different supplement dosing plans and potentially different supplementation durations into one intervention group • No comparison of baseline characteristics between control and intervention groups; genotypes or risk levels of controls unknown • Statistical analysis methods NR • Power calculation NR		
Saccone, 2016[19] **NRCT; Italy** **Summary:** In pregnant women with prior preeclampsia, consuming 15 mg/d 5-MTHF was associated with lower incidence of overall preeclampsia, severe preeclampsia, early-onset preeclampsia, and late-onset preeclampsia compared to no 5-MTHF supplementation. **Limitations:** • Control group declined 5-MTHF mostly for economic reasons • No preregistered protocol with analysis plan; results reported for multiple subgroups • Power calculation NR	Maternal intake of 15 mg/d 5-MTHF supplementation; from <14 wk gestation through delivery; 2 groups: • Control: aspirin alone (Ref, n=146) • Intervention:15 mg/d 5-MTHF + aspirin (n=157)	**Incidence of overall PE**, Chi-square or Fischer exact test, **P=0.019** • Control: n=58 (39.7%) • 5-MTHF: n=34 (21.7%), OR=0.57, 95% CI: 0.25, 0.69 **Incidence of mild PE**, Chi-square or Fischer exact test, **P=0.022** • Control: n=45 (30.8%) • 5-MTHF: n=29 (18.5%), OR=0.37, 95% CI: 0.18, 0.74 **Incidence of severe PE**, Chi-square or Fischer exact test, **P=0.041** • Control: n=13 (8.9%) • 5-MTHF: n=5 (3.2%), OR=0.44, 95% CI: 0.12, 0.97 **Incidence of early-onset PE**, Chi-square or Fischer exact test, **P=0.033** • Control: n=11 (7.5%) • 5-MTHF: n=3 (1.9%), OR=0.34, 95% CI: 0.07, 0.87 **Incidence of late-onset PE**, Chi-square or Fischer exact test, **P=0.023** • Control: n=47 (32.2%)

Article	Intervention/Exposure	Outcome and Results
		• 5-MTHF: n=31 (19.7%) OR=NR **<u>Sub-analysis of women without medical conditions:</u>** **Incidence of overall PE**, Chi-square or Fischer exact test, **P<0.05** • Control: 39.3% • 5-MTHF: 20.2%, OR=0.51, 95% CI: 0.32, 0.82 **Incidence of severe PE**, Chi-square or Fischer exact test, **P<0.05** • Control: 11.2% • 5-MTHF: 3.0%, OR=0.10, 95% CI: 0.03, 0.33 **Incidence of early-onset PE**, Chi-square or Fischer exact test, **P<0.05** • Control: 10.1% 5-MTHF: 2.0%, OR=0.20, 95% CI: 0.04, 0.90
Cohort Studies		
Catov, 2009 [20] **PCS (DNBC); Denmark** **Summary:** Folic acid supplementation during the periconceptional period is not associated with the risk of preeclampsia **Limitations:** • Exposure based on self-report at recruitment; Participants may have changed supplementation during pregnancy • No preregistered protocol with analysis plan	Maternal intake of folic acid supplements during periconceptional period (4 wk before LMP – 8 wk after LMP); 2 groups: • Non-users (Ref, n=7582) • FA-only users (n=2468)	**Risk of PE among all women**, Cox regression, P=NS • Non-users: (Ref) • FA during pre- and post-conception (4 wk before LMP – 8 wk after LMP): HR=0.98, 95% CI: 0.50, 1.92 • FA during post-conception only (3 wk after LMP – 8 wk after LMP): HR=0.95, 95% CI: 0.55, 1.66 **Risk of PE among normal-weight women**, Cox regression, P=NS • FA during post-conception only: HR=0.80, 95% CI: 0.51, 1.26
Vanderlelie, 2016 [21] **PCS (EFHL); Australia** **Summary:** Consuming folic acid supplements during the first trimester was associated with significantly reduced odds of	Maternal intake of folic acid supplements during first trimester; 2 groups: • No supplement (Ref, n=1066) Folate only (n=476)	**Prevalence (%) and Adjusted Odds Ratio (AOR) of preeclampsia**: • All (n=1542): ○ No supplement (Ref): 2.9% ○ Folate only: 1.26%; AOR: 0.42, 95% CI: 0.13, 0.98 • BMI <25 (n=1305*): ○ No supplement (Ref): 1.87%

Article	Intervention/Exposure	Outcome and Results
preeclampsia compared to not consuming a supplement in the full study population as well as for those with a prepregnancy BMI ≥25. **Limitations:** • Not all key confounders accounted for • Dose, duration of FA supplementation unknown • Self-report of supplementation from different stages of pregnancy (some retrospectively); Participants may have changed supplementation during pregnancy • Study registered but no preregistered analysis plan		○ Folate only: 1.14%; AOR: 0.72, 95% CI: 0.39, 1.35 • BMI ≥25 (n=956*): ○ No supplement (Ref): 4.6% ○ Folate only: 2.36%; AOR: 0.55, 95% CI: 0.31, 0.96 *Note: N includes 3 groups: (1) No supplement, (2) Folate only, and (3) Multivitamin. Results for Multivitamin was not included in this table (not relevant to SR question)
Wen, 2016 [22] **PCS (OaK); Canada** **Summary:** Consuming folic acid supplements compared to no supplements during 12-20wk gestation was associated with lower risk of preeclampsia among high-risk women, but the difference was not statistically significant among low-risk women or women overall. **Limitations:** • Exposure based on self-report at enrollment which varied between 8 – 20 GW • Dose, duration of FA supplementation unknown; Participants may have changed supplementation during pregnancy • Few participants consumed no supplements or folic acid alone	Maternal intake of folic acid supplements; at 12-20wk gestation; 2 groups: • No supplement (Ref, n=404) • FA alone (n=625)	**Preeclampsia in all women**, Multiple logistic regression: • No supp (Ref): n=17 (4.2%) • FA alone: n=24 (3.8%); OR=0.76, 95% CI: 0.36, 1.62 **Preeclampsia in low-risk women** (n=899). Multiple logistic regression: • No supp (Ref, n=348)): n=9 (2.6%) • FA alone (n=551): n=18 (3.3%), OR=1.35, 95% CI: 0.52, 3.51 **Preeclampsia in high-risk women** (BMI ≥35, previous preeclampsia history, chronic hypertension, diabetes, multiple pregnancy, n=130), Multiple logistic regression: • No supp (Ref; n=56): n=8 (14.3%) • FA alone (n=74): n=6 (8.1%), OR=0.17, 95% CI: 0.03, 0.95

Article	Intervention/Exposure	Outcome and Results
resulting in low power • No preregistered protocol with analysis plan		

Table 13. Risk of bias for randomized controlled trials examining folic acid from dietary supplements and/or fortified foods during pregnancy and risk of hypertensive disorders of pregnancy[xxix, xxx]

	Randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Manizheh, 2009[16]	Some concerns	Low	Low	Low	Some concerns
Sayyah-Melli, 2016[17]	Low	Low	Some concerns	Low	Some concerns
Shahraki, 2016[18]	Low	Low	Low	Low	Some concerns

Table 14. Risk of bias for non-randomized controlled trials examining folic acid from dietary supplements and/or fortified foods during pregnancy and risk of hypertensive disorders of pregnancy[xxxi]

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of the reported result
Li, 2015[15]	Serious	Serious	Moderate	No Information	No Information	No Information	Moderate
Saccone, 2016[19]	Serious	Low	Low	Low	Low	Low	Moderate

[xxix] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[xxx] Possible ratings of low, some concerns, or high determined using the "Cochrane Risk-of-bias 2.0" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

[xxxi] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool" (Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.)

Table 15. Risk of bias for observational studies examining folic acid from dietary supplements and/or fortified foods during pregnancy and risk of hypertensive disorders of pregnancy[xxxii]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Catov, 2009[20]	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Vanderlelie, 2016[21]	Serious	Low	Moderate	Moderate	Low	Low	Moderate
Wen, 2016[22]	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate

[xxxii] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

Systematic review question—Human milk composition

What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and human milk composition?

Conclusion statements and grades

Pregnancy

No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed before and during pregnancy and human milk folate. (Grade: Grade not assignable)

Lactation

Moderate evidence indicates that folic acid supplements consumed during lactation does not influence folate levels in human milk. (Grade: Moderate)

No evidence is available to determine the relationship between folic acid from fortified foods consumed during lactation and human milk folate. (Grade: Grade not assignable)

Summary of the evidence

Pregnancy

- No studies related to folic acid intake from supplements during pregnancy which met the criteria for inclusion in this systematic review were identified through a literature search from 1980 to 2019.

Lactation

- Four studies were identified through a literature search from 1980 to 2019, which met the criteria for inclusion in this systematic review: 3 RCTs and 1 uncontrolled before-and-after study.[11,12,14,23]
- Studies varied in intervention details, including folic acid supplement type (folic acid, 5-MTHF, or pteroylmonoglutamate), dose (300 µg/d, 400 µg/d, or 1 mg/d), time of initiation (1 to 25 weeks postpartum), duration (4 weeks, 12 weeks, or 16 weeks), and sample characteristics.
- As defined by the inclusion criteria, all studies took place in high or very high Human Development Index countries; therefore, the participants were likely to be folate replete.
- None of the studies found an association between folic acid supplementation in women who were lactating and milk folate levels.
- This body of evidence had important limitations:
    - In one of the 3 RCTs, the reference group was not recruited and randomized with the other 2 study groups. In another study, milk folate was significantly different between the control and intervention groups at baseline, and this was not controlled for in the analyses.
    - Only 1 study reported a power calculation and that study did not reach the target sample size.
    - The study populations did not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.

Description of the evidence

This systematic review included articles that address the relationship between folic acid from supplements and/or fortified foods[ii] consumed before and during pregnancy and lactation and human milk composition (**Figure 4**). The search included articles from countries categorized as high or very high on the Human Development Index[iii] and published between January 1980 and June 2019. Studies included generally healthy women up to 6 months before pregnancy, during pregnancy or lactation at the time of the intervention or exposure. Study designs that were included were: randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), prospective and retrospective cohort studies, nested case-control studies, uncontrolled before-and-after studies, and cross-sectional studies. Due to changes in human milk composition during the first weeks after delivery (e.g., colostrum, transitional milk), only studies assessing milk folate levels in mature milk (defined as milk produced ≥2 weeks after delivery) were included.

Four studies were included in the body of evidence (see **Figure 6**).[11,12,14,23] Basic characteristics of the studies are shown in **Table 16**. Three studies were RCTs[11,12,23] and 1 was an uncontrolled before-and-after design.[14] Two studies were conducted in Canada,[11,23] 1 in the United States[12] and 1 in Japan.[14]

Participant characteristics

There was some variation in participant characteristics. Two studies, one from Canada and one from the United States, included women with mean ages of 32 and 34 years, respectively.[12,23] The majority of these women had college degrees and were of relatively high socioeconomic status. Another study from Canada was in adolescent girls with a mean age of 17 years,[11] and predominantly of low socioeconomic status. One study in Japan did not provide additional information on participant characteristics.[14]

Interventions/Exposures

All 4 studies were experimental studies examining the relationship between folic acid supplementation during lactation on human milk folate levels. The dose, duration and timing of initiation of the intervention varied across the studies. Folic acid supplement dose varied from 300 µg/d[11] to 1 mg/d.[12,14] One study included a study arm with 400 µg/d 5-MTHF in addition to an arm with 400 µg/d of folic acid.[23] Supplementation lasted 4,[14] 12,[11,12] or 16 weeks.[23] Two studies began the intervention within a week from birth,[11,23] 1 study began 3 months postpartum,[12] and 1 study began the intervention in women between 3 and 25 weeks postpartum.[14]

No studies met the inclusion criteria related to folic acid intake from fortified foods on human milk folate.

Evidence synthesis

Four experimental studies examining the relationship between folic acid supplementation during lactation on human milk folate were included in this review. Three of these studies were placebo-controlled RCTs,[11,12,23] 2 of which were double-blind.[11,12] One study was an uncontrolled before-and-after design (see **Table 16**).[14] Despite differences in folic acid dose, type, time of initiation, duration, and populations

studied, no study found a significant effect of folic acid supplementation on milk folate levels (see **Table 17**).

Within this body of evidence, 3 doses of folic acid were assessed: 300 µg/d,[11] 400 µg/d,[23] and 1 mg/d.[12,14] At each dose, there was no significant difference in milk folate between supplemented women and women taking a placebo.

Different forms of folic acid supplementation were tested. Houghton[23] compared supplementation of 400 µg/d 5-MTHF to an equal dose of folic acid or a placebo and found no difference in milk folate levels after supplementation. Further, milk folate levels did not change after taking 1 mg/d of a synthetic folic acid supplement (pteroylmonoglutamate) for 4 weeks compared to milk folate levels before supplementation in the same sample.[14]

Time of initiation and duration of supplementation also varied across studies. Two studies began supplementing lactating women within 1 week from delivery; the durations lasted 12 weeks[11] and 16 weeks.[23] Mackey[12] initiated supplementation at 3 months postpartum and the study had a 12-week duration. Timing of initiation in the uncontrolled before-and-after study ranged from 3 to 25 weeks postpartum and lasted 4 weeks. Regardless of time of initiation or duration of supplementation, none of the folic acid interventions resulted in a significant difference in milk folate.

While the outcome of interest was milk folate levels, one study also measured folate-binding protein and unmetabolized folic acid in milk.[23] After 16 weeks of 400 µg/d folic acid or 5-MTHF supplementation, there was no difference in these outcomes between the two intervention groups or compared to a placebo group.

Finally, there were some differences in study populations. Two studies included women with a mean age of 32 and 34 years, respectively,[12,23] while one study only enrolled adolescents with a mean age of 17 years.[11] In two studies, participants were predominantly White women who were well-educated and of relatively high socioeconomic status.[12,23] The adolescent population from the Keizer[11] study was mostly of lower socioeconomic status. Keizer[11] and Tamura[14] did not report race/ethnicity but the Tamura study took place in a Japanese population.

Each study had limitations to be considered (**Table 16, Table 17, Table 18, and Table 19**). The only study that reported a power calculation had 21 percent attrition resulting in group sample sizes less than the target number determined by the power calculation.[23] For the same study, the randomization and blinding methods were not clearly reported and the reference group was not recruited and randomized with the other two study groups. In the RCT by Mackey et al,[12] while participant characteristics did not differ between groups, there was a difference in milk folate levels at baseline, such that the control group had significantly higher milk folate compared to the intervention group. This indicates that there was an issue with the randomization process and makes interpretation of results problematic. Keizer et al[11] did not account for most of the key confounders and did not provide information on missing data. Tamura et al[14] did not include a control group, reported very little information on participant characteristics and no information on statistical analyses conducted. Publication bias is always a concern; however, given that these studies were small in size and have null findings, publication bias is not a serious concern with this evidence.

Despite limitations and differences in intervention details, findings were consistent across studies. The studies were conducted only with lactating women, while no studies examined the effect of folic acid supplementation before or during pregnancy or the effect of folic acid from fortified foods on the outcome of interest. The analytic sample size in these 4 studies ranged from 16[14] to 57,[23] with group samples ranging from 14 to 23. Only one study conducted a power calculation (based on blood folate as the outcome) and that study did not reach the target sample size.[23] The study populations do not fully represent the racial/ethnic or socioeconomic diversity of the U.S. population.

Assessment of the evidence[xxxiii]

The conclusion statement "evidence indicates that folic acid supplements consumed during lactation does not influence folate levels in human milk" was graded as **moderate**. As outlined and described below, the body of evidence examining consumption of folic acid supplements during lactation and folate levels in human milk was assessed for the following elements used when grading the strength of evidence:

- **Risk of Bias**: For the RCTs, there were some concerns of risk of bias suggesting a moderate likelihood that the design and conduct of the studies prevented or minimized bias such that the reported results are the true effects of the intervention and plausible bias and/or potential limitations are unlikely to alter the results. These concerns were mostly from bias due to randomization[12,23] and missing outcome data.[23] For the uncontrolled before-and-after study,[14] there was a limited likelihood that the design and conduct of the studies prevented or minimized bias such that the reported results may not be the true effects of the intervention/ exposure, and plausible bias and/or potential limitations may have altered the results. Risk of bias was primarily attributed to bias due to confounding, classification of interventions, and selection of the reported result.
- **Consistency**: For RCTs and uncontrolled before-and-after studies, consistency was considered strong such that supplementation of folic acid during lactation did not result in significant differences in milk folate levels compared to a placebo-control group or compared to milk folate levels before the intervention. Non-significant findings were consistent across studies despite differences in intervention dose, duration, and time of initiation postpartum.
- **Directness**: This systematic review question had multiple components (e.g., folic acid from supplements and/or fortified foods; and, before and during pregnancy and during lactation). The evidence focusing on folic acid supplementation during lactation directly aligned with the corresponding part of the systematic review question and was rated as strong.
- **Precision**: Based on the distribution of means and variance (standard deviation and standard error), the RCTs were considered strong for precision. Precision could not be assessed for the uncontrolled before-and-after study because there was only 1

[xxxiii] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

study.[14]

- **Generalizability**: For RCTs and the uncontrolled before-and-after study, generalizability was considered limited. Most studies were in White women; half (2 of the 4 studies) had a majority of women with college degrees and were of relatively high socioeconomic status.[11,12] One study was in adolescents who were of low socio-economic status[11]; and one study was in Japanese women with no information on participant characteristics.[14]

Table 16. Description of studies examining the relationship between consumption of folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and folate levels in human milk[xxxiv,xxxv]

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Randomized Controlled Trials		
Houghton, 2009[23] **RCT; Canada** **Baseline N=72** **Analytic N=57 (Attrition: 21%)** **Baseline characteristics:** • Maternal age: 32±4y • SES: ○ Education: Community college or university degree: 93% ○ Annual Family Income: ≥$75,000/y: 76% • Smoking status: 0% • Parity: Placebo group: 0.5±0.6, FA: Mean group=0.7±0.9, 5-MTHF group: 0.6±0.8, P=NS • GA: 36wk • MTHFR status: 5-MTHF: CC: 41%, CT: 45%, TT: 14%, FA: CC: 37%, CT: 46%, TT: 17%, Placebo: CC: 43%, CT: 35%, TT: 22% • Prenatal folic acid supplement: Placebo group: 948±207 µg/d, FA group: 935±229 µg/d, 5-MTHF group: 886±273 µg/d, P=NS **Funding Sources:** Merck Eprova AG (Schaffhausen, Switzerland); Natural Sciences & Engineering Research Council of Canada; Canadian Institute of Health Research Training Grant in Clinical Nutrition; Ontario Student Opportunity Trust	**Exposure:** Maternal intake of folic acid from supplements, 1-16wk postpartum; 3 groups: • Placebo (n=23) • 400 µg/d folic acid (n=21) • 400 µg/d 5-MTHF (n=22) *Exposure assessment method:* Folate content of supplements was verified analytically. Supplemental folate intakes were determined by assessing the difference between the number of capsules dispensed at randomization (<1wk postpartum) and at 16wk postpartum. In addition, all participants received a daily multivitamin and mineral supplement (1 mg vit B6, 3 µg vit B_{12}, and 4 mg ferrous fumarate), and the participants agreed not to consume any other folate-containing vitamin or mineral supplement during the course of the study. **Outcome:** • Total milk folate measured at 4, 8, and 16wk postpartum • Unmetabolized milk folic acid at 16wk • Soluble milk folate binding protein (FBP) concentrations at 16wk	**Confounders accounted for:** • Maternal age: No baseline differences • SES: No baseline differences • Smoking Status: 100% Non-smokers • Parity: No baseline differences **Not accounted for:** • Key confounders: Race/ethnicity, Anthropometry • Other factors to be considered: Gestational age **Limitations:** • Unclear randomization and blinding methods; reference group recruited separately, not part of randomization • Some missing data with potential differences between groups, resulting in group sample sizes smaller than estimate from power calculation

[xxxiv] Values indicate mean± standard deviation unless otherwise stated

[xxxv] d: day; FA: folic acid; GA: gestational age; mo: month(s); MTHF: methyltetrahydrofolate; NR: not reported; NS: non-significant; RCT: randomized controlled trial; SES: socioeconomic status; SEM: standard error of the mean; USDA: United States Department of Agriculture; wk: week(s); y: year(s)

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Fund, The Hospital for Sick Children Foundation Scholarship Program	*Outcome assessment method:* Complete breast expression (manually or by electric breast pump) at 1300-1450. Measured by microbiological assay using *L. rhamnoses*.	
Keizer, 1995[11] **RCT; Canada** **Baseline N=29** **Analytic N=29 (Attrition: 0%)** Note: a third study group in formula-feeding mothers was not included in this table (not relevant to SR question) **Baseline Characteristics:** • Maternal age: 17.0y, SEM=0.17 (range 14.0-19.0y) • Race/Ethnicity: ○ White: 92% ○ Native Canadian/White: 4% ○ Black: 3% ○ Asian/White: 1% • SES: ○ Predominantly low SES ○ Main source of income: Government: 56%, Parent or guardian: 39%, Employment: 5% • GA: 36wk; Infant born <37 wk gestation: 0% • Substance use: "Negligible" • Folate deficiency: 59% consumed <67% of recommended nutrient intake **Funding Sources:** Natural Sciences and Engineering Research Council of Canada	**Exposure:** Maternal intake of folic acid supplements from 1 - 12 wk postpartum; 2 groups: • Control: placebo (cornmeal-sucrose; n=15) • Intervention: 300 µg/d folic acid (n=14) *Exposure assessment method*: Double-blind design: supplements and placebo were visually indistinguishable; research assistants and participants were unaware of the contents of the capsules; Participants were instructed to avoid the consumption of additional vitamin and mineral supplements during the postpartum period. Adherence was calculated by determining the difference in the number of capsules provided at the beginning and those remaining at the end of each 4-wk period. **Outcome:** Milk folate at 4, 8, and 12wk postpartum *Outcome assessment method*: All milk from a single breast was expressed manually or by electric breast pump; collected between 1300 and 1450. Total milk folate concentrations were measured microbiologically by using *L. casei*.	**Confounders accounted for:** • Maternal age: 100% adolescents (14-19y) **Not accounted for:** • Key confounders: Race/ethnicity, SES, Anthropometry, Smoking, Parity • Other factors to be considered: Gestational age **Limitations**: • No information on missing data for continuous outcomes or multiple analyses • No accounting for most key confounders • Power analysis NR
Mackey, 1999[12] **RCT; United States**	**Exposure:** Maternal intake of folic acid from supplements from 3mo to 6mo postpartum;	**Confounders accounted for:** • Maternal age: NS between groups • Race/ethnicity: 100% White

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Baseline N=42 **Analytic N=42 (Attrition: 0%)** **Baseline Characteristics:** • Maternal age: 34y (range 26-42y) • Race/Ethnicity: White: 100% • SES: ○ 72±1.6 (scores in 60s to 70s are associated with professional, technical, and managerial workers) ○ Maternal education: 16±0.5y • BMI at 3mo postpartum (baseline): 25±1 • Parity: 2 • Prenatal supplement: 0.9 mg/d • GA: infants born full-term (37-40wk) **Funding Sources:** USDA	2 groups: • Control: 0 mg/d folic acid (n=21) • Intervention: 1 mg/d folic acid (n=21) *Exposure assessment method**:*** Double-blind design: All participants received either 1 mg folic acid/d (intervention) or a placebo tablet (0 mg folic acid/d, control) and the same multivitamin and mineral supplement (2500 IU vit A, 60 mg vit C, 400 IU vit D, 30 IU vit E, 1.5 mg thiamine, 1.7 mg riboflavin, 20 mg niacinamide, 2 mg vit B6, 6 µg vit B_{12}, 300 µg biotin, 10 mg pantothenic acid, 9 mg Fe, 150 µg I, 3 mg Zn, 2.5 mg Mn, 25 µg Cr, 25 µg Mo). Adherence defined as successfully taking >80% of monthly allotments of folic acid supplementation. **Outcome:** Milk folate from samples collected at 3mo (baseline) and 6mo postpartum *Outcome assessment method:* Each milk sample (15-30 mL) collected via complete breast expression by manual or mechanical pump. Time of expression NR. Samples were handled under gold light to prevent photooxidization. Milk folate content was measured in a microbiological assay with *L. casei*.	• SES: NS between groups • Anthropometry: NS between groups • Smoking Status: 100% nonsmoking • Parity: NS between groups • GA: 100% infants born full term (37-40 weeks) **Limitations**: • Milk folate concentrations differed by group at baseline • Power analysis NR • Baseline N not clear • Human milk collection details NR: time of day
Uncontrolled Before-and-After Study		
Tamura, 1980[14] **Uncontrolled Before-and-After; Japan** **Baseline N=16** **Analytic N=16 (Attrition: 0%)**	**Exposure:** Maternal intake of folic acid from supplements; 1 group: 1mg/d synthetic (PteGlu) for 4wk, starting 3-25wk postpartum in lactating mothers	**Confounders accounted for:** • SES: all from same SES group **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, Anthropometry, Smoking, Parity

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Baseline Characteristics: • Child age: range 3-25wk • SES: All participants belonged to the same socioeconomic group **Funding Sources:** United States-Japan Medical Cooperation Program	• Baseline (n=16) • Follow-up (n=16): after 4wk intervention period *Exposure assessment method*: NR **Outcome:** Milk folate in samples collected at baseline (3-25wk postpartum) and after intervention, 4wk later *Outcome assessment method*: Milk samples collected just before babies were fed in the early afternoon (~2:00-3:00pm); ~10ml manually expressed into test tubes. Folate levels were determined by microbiological assay using *L. casei*.	• Other factors to be considered: Gestational age **Limitations**: • No control group • Power analysis NR • No report of statistical analysis

Table 17. Results from studies that examined the relationship between folic acid intake from dietary supplements and/or fortified foods during pregnancy and lactation and folate levels in human milk[xxxvi, xxxvii]

Article	Intervention/Exposure	Outcome and Results
Randomized Controlled Trials		
Houghton, 2009[23] **RCT; Canada** **Summary:** Consuming folic acid supplements as either folic acid or 5-MTHF compared to a placebo from 1 to 16 weeks postpartum did not affect total milk folates (at 4, 8, and 16 weeks postpartum), unmetabolized milk folic acid (at 16 weeks postpartum), or milk folate binding protein concentrations (at 16 weeks postpartum). **Limitations:** • Unclear randomization and blinding methods; reference group recruited separately, not part of randomization • Some missing data with potential differences between groups, resulting in group sample sizes smaller than estimate from power calculation	Maternal intake of folic acid from supplements, 1 - 16wk postpartum; 3 groups: • Placebo (n=23) • FA: 400 µg/d folic acid (n=21) • 5-MTHF: 400 µg/d 5-MTHF (n=22)	**Milk folate (Mean±SD):** repeated-measures ANOVA, P>0.05 • Placebo: 4wk: 193±62 nmol/L, 8wk: 207±76 nmol/L, 16wk: 183±57 nmol/L • FA: 4wk: 155±55 nmol/L, 8wk: 176±80 nmol/L, 16wk: 159±79 nmol/L • 5-MTHF: 4wk: 189±52 nmol/L, 8wk: 175±43 nmol/L, 16wk: 182±102 nmol/L **Folate-binding protein (Mean±SD) at 16wk:** one-factor ANOVA, P>0.05 • Placebo: 40.9±13.4 nmol/L • FA: 43.0±14.3 nmol/L • 5-MTHF: 41.5±16.3 nmol/L **Unmetabolized milk folic acid at 16wk:** • Pooled mean±SD =14.4±9.7 nmol/L, P>0.05
Keizer, 1995[11] **RCT; Canada** **Summary:** Consuming folic acid supplements (300 µg/d) compared to a placebo from 1 week to 12 weeks postpartum did not	Maternal intake of folic acid from supplements, from 1wk to 12wk postpartum; 2 groups: • Control: placebo (n=15) • Intervention: 300 µg/d folic acid (n=14)	**Milk folate (nmol/L, N=29):** Split-plot analysis, No differences between groups or across time • 4wk: Mean=114.9, SEM=16.5, Median=104.0, IQR=64.1, 146.0 • 8wk: Mean=124.6, SEM=20.4, Median=116.7, IQR=65.9, 156.3 • 12wk: Mean=83.8, SEM=29.2, Median=129.6, IQR=75.4, 159.1

[xxxvi] ANOVA: analysis of variance; d: day; IQR: interquartile range; mo: month(s); MTHF: methyltetrahydrofolate; NR: not reported; NS: non-significant; RCT: randomized controlled trial; SD: standard deviation; SEM: standard error of the mean; wk: week(s)
[xxxvii] Statistically significant findings bolded

Article	Intervention/Exposure	Outcome and Results
influence milk folate concentration at 4, 8, or 12 weeks postpartum. **Limitations:** • No information on missing data for continuous outcomes or multiple analyses • No accounting for most key confounders • Power analysis NR		
Mackey, 1999[12] **RCT; United States** **Summary:** Consuming folic acid supplements (1 mg/d) compared to a placebo from 3 months to 6 months postpartum did not result in a difference in milk folate content at 6 months postpartum. Note: milk folate levels differed by group at baseline. **Limitations:** • Milk folate concentrations differed by group at baseline • Power analysis NR • Baseline N not clear • Human milk collection details NR: time of day	Maternal intake of folic acid from supplements from 3mo (baseline) to 6mo postpartum; 2 groups: • Control (0 mg/d folic acid; n=21) • Intervention (1 mg/d folic acid; n=21)	**Milk folate (nmol/L):** Time difference (within group), one-way ANOVA Control group (0mg): **3mo > 6mo: P<0.02** • 3mo (baseline): Mean=224.4 nmol/L, SEM=11.6 • 6mo: Mean=187.0 nmol/L, SEM=11.9 Intervention group (1mg): 3mo vs 6mo: P>0.05 • 3mo (baseline): Mean=186.2 nmol/L, SEM=9.6 • 6mo: Mean=181.9 nmol/L, SEM=10.6 Between group, repeated-measures ANOVA and ANCOVA • At 3mo (baseline): **Control > Intervention, P<0.05** • At 6mo: P>0.05 Time*Group difference: NR
Uncontrolled Before-and-After Studies		
Tamura, 1980[14] **Uncontrolled Before-and-After; Japan** **Summary:** Consuming folic acid supplements (1mg/d) for 4 weeks in the postpartum period was associated with increased plasma and red blood cell folate levels,	Maternal intake of folic acid from supplements; 1 group: 1mg/d synthetic (PteGlu) for 4wk, starting 3-25wk postpartum in lactating mothers • Baseline (n=16) • Follow-up (n=15): after 4wk intervention period	**Milk folate (mean):** statistical analyses NR, P>0.6 • Baseline (n=16): 130.2±45.9 ng/ml • Follow-up (n=15): 136.6±41.2 ng/ml

Article	Intervention/Exposure	Outcome and Results
but not milk folate levels in lactating mothers. **Limitations:** • No control group • Power analysis NR • No report of statistical analysis		

Table 18. Risk of bias for randomized controlled trials examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and human milk composition[xxxviii, xxxix]

	Randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Houghton, 2009[23]	Some Concerns	Low	High	Low	Low
Mackey, 1999[12]	High	Low	Low	Low	Low
Keizer, 1995[11]	Low	Low	Low	Low	Low

Table 19. Risk of bias assessment for non-randomized studies of interventions examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and human milk composition[xl]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Tamura, 1980[14]	Serious	Low	Moderate	Low	Low	Low	Moderate

[xxxviii] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[xxxix] Possible ratings of low, some concerns, or high determined using the "Cochrane Risk-of-bias 2.0" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

[xl] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool" (Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.)

Systematic review question—Developmental milestones, including neurocognitive development, in the child

What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

Conclusion statements and grades

Pregnancy

Insufficient evidence is available to determine the relationship between folic acid supplementation before and/or during pregnancy and cognitive, language, and social-emotional development, and risk of autism spectrum disorder in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between folic acid from supplements consumed before and during pregnancy and movement and physical development, academic performance, anxiety, depression, or the risk of attention-deficit disorder or attention-deficit/hyperactivity disorder in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between folic acid from fortified foods consumed before and during pregnancy and developmental milestones, including neurobehavioral development, in the child. (Grade: Grade not assignable)

Lactation

No evidence is available to determine the relationship between folic acid from supplements or fortified foods consumed during lactation and developmental milestones, including neurobehavioral development, in the child. (Grade: Grade not assignable)

Summary of the evidence

Pregnancy

- Six articles that met the criteria for inclusion in this systematic review was identified through a literature search from 1980 to 2019.[24-29] The articles report findings from 4 studies representing 4 outcome domains:
    - Cognitive development: 1 RCT; 2 articles.
    - Language and communication development: 1 PCS; 2 articles.
    - Social-emotional development: 1 RCT; 1 article.
    - ASD: 1 nested case-control study; 1 article.
- Generally, folic acid supplementation before or during pregnancy was either not associated with or had a beneficial association with the included outcomes.
- For cognitive development, findings were inconsistent; therefore a conclusion statement could not be drawn.
- For social-emotional development, only 1 study was available and it had some limitations; therefore, a conclusion could not be drawn.
- For language development, 2 articles were included from the Norwegian Mother and Child (MoBa) cohort. These articles reported a lower risk of severe language delay in children age 3 years whose mothers had taken folic acid supplements during

early pregnancy compared to children whose mothers either did not take folic acid during pregnancy or took folic acid supplements later in pregnancy.
- For ASD, 1 nested case-control found a significant association between folic acid supplementation before pregnancy and during pregnancy and lower risk of ASD in children ages 8 to 12 years, compared to no folic acid supplementation. This was true for a number of subgroups within the sample, including children without siblings, males, females, children with low socioeconomic status, children with both parents with psychiatric diagnosis, and children without intellectual disabilities.
- No evidence was found on whether folic acid supplementation before and/or during pregnancy was associated with other included outcomes: movement and physical development, academic performance, ADD or ADHD, anxiety, or depression.
- No evidence was found on folic acid from supplements or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development.

Lactation

- The search identified 0 studies published between 1980 and 2019 that met the inclusion criteria.

Description of the evidence

This systematic review included articles that address the relationship between folic acid from supplements and/or fortified foods[ii] consumed before and during pregnancy and developmental milestones, including neurocognitive development, in the child. The search included articles from countries categorized as high or very high on the Human Development Index[iii] and published between January 1980 and July 2019. Studies included generally healthy women up to 6 months before pregnancy and during pregnancy at the time of the intervention or exposure. Study designs that were included were: randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), prospective and retrospective cohort studies, and nested case-control studies.

The outcomes for this systematic review include developmental domains of the child (including cognitive, language/communication, movement/physical, and social-emotional domains), academic performance, attention deficit disorder (ADD) or attention deficit/hyperactivity disorder (ADHD), anxiety, depression, and autism spectrum disorder (ASD). Outcome measures were included for children from birth to age 18 years.

This body of evidence included 6 articles from 4 studies (**Table 20; Figure 8**). There were 3 articles from 2 RCTs: 1 article from the Folic Acid Supplementation in the Second and Third Trimester (FASSTT) study[26] and 2 articles from the Nutraceuticals for a Healthy Life (NUHEAL) study.[24,25] There were 2 articles from the Norwegian Mother and Child Cohort (MoBa) prospective cohort study[27,28] and 1 article from a nested-case control study.[29] The FASSTT study was conducted in the United Kingdom,[26] the NUHEAL study was conducted in Germany, Hungary, and Spain,[24,25] the MoBa study was conducted in Norway,[27,28] and the nested case-control study was conducted in Israel.[29]

Participant characteristics

The studies all took place in Europe (the United Kingdom, Germany, Hungary, Spain,

and Norway) and Israel (none of which have mandatory fortification of folic acid) and most of the participants being in their late 20s or early 30s. Race/ethnicity data were only reported in 1 article (100 percent White).[26] In terms of socioeconomic status, 77 percent of participants in the FASSTT RCT were homeowners,[26] while 60 percent of participants from the nested case-control study were considered "low socioeconomic status" with no further description.[29] Most women across the studies were educated for at least 12 years and/or qualified for a university. Only the RCTs reported type of infant feeding[28]; of these, ~47 percent of infants were human milk fed as opposed to formula- or mixed fed.

Intervention/Exposure

The exposures varied across the studies. In the FASSTT RCT, women were provided with a placebo or folic acid supplement (400 µg) every day from 14 weeks gestation through delivery.[26] Women were only included in this study if they consumed folic acid supplements during their first trimester. Women in the NUHEAL RCT were only included if they *did not* take folic acid supplements prior to the start of the study at 20 weeks gestation.[24,25] Another difference between the RCTs was the form of folate supplementation. The NUHEAL study tested the effect of supplementation of 5-MTHF rather than folic acid.[24,25] Using a double-blind, 2x2 factorial design, NUHEAL was designed to test the effects of long chain polyunsaturated fatty acids and folate supplementation on developmental outcomes. Women were randomized into 1 of 4 groups: placebo, 5-MTHF (400 µg/d), Fish oil (500 mg/d DHA, 150 mg/d EPA), and 5-MTHF+Fish oil (400 µg/d 5-MTHF, 500 mg/d DHA, 150 mg/d EPA).

Within the observational studies, the exposure was folic acid supplementation before and/or during pregnancy. The MoBa cohort provided data on women who took folic acid supplements in early pregnancy (4 weeks before pregnancy to 8 gestational weeks), in later pregnancy (9 to 29 weeks gestation), and women who did not take folic acid supplements before or during pregnancy.[27,28] Levine et al[29] had data from women's folic acid supplementation before pregnancy (271 to 540 days before delivery; in other words, 0 to 9 months before conception) and anytime during pregnancy. Exposure data were also combined to look at folic acid supplementation before and during pregnancy. The comparator group included children whose mothers did not take folic acid supplementation either before or during pregnancy.

Outcome

The studies differed in terms of outcome, specifically child age at outcome assessment and the outcome domain related to developmental milestones and neurocognitive development. The FASSTT RCT measured social-emotional/behavioral traits when children were 7 years old using parent-reported questionnaires (Resilience (RASP), Strengths and Difficulties questionnaire (SDQ), and Emotional intelligence (TEIQue-CSF)).[26] The studies from the NUHEAL trial reported outcomes of cognitive function when children were 6.5 years old (intelligence[24]) and 8.5 years old (attention and executive function[25]). Both papers from the MoBa cohort report language competency at 3 years,[27,28] and the outcome for the nested case-control study by Levine et al[29] was autism spectrum disorder diagnosis with and without comorbid intellectual disability.

Outcome assessment methods

Henry et al[26] evaluated child social-emotional development at age 7 years with maternal report on three validated scales: the Strengths and Difficulties Questionnaire

(SDQ), the Resiliency Attitudes and Skills Profile (RASP), and the Trait Emotional Intelligence Questionnaire Child Short Form (TEIQue-CSF). The SDQ is a widely-used tool to assess child problems, and is comprised of 5 scales: Conduct Problem, Hyperactivity, Emotional Symptoms, Peer Problems, and Prosocial Behavior. The RASP measures 7 dimensions of resilience, including creativity, humor, independence, initiative, insight, relationships and values orientation, and the TEIQue-CSF assesses emotional intelligence.

The NUHEAL study assessed child intelligence at age 6.5 years with the Kaufman Assessment Battery for Children (K-ABC[24]) and attentional network development, including attention and executive functioning, at age 8.5 years with the Attention Network Test (ANT[25]). The K-ABC is a widely-used, standardized scale which includes the Mental Processing Composite, a measure similar to the intelligence quotient, and is comprised of the Simultaneous and Sequential Processing Scales. The Simultaneous Processing Scale examines problem-solving skills that require processing of many stimuli at once. The Sequential Processing Scale, which primarily measures short-term memory, consists of subtests that evaluate children's ability to solve problems that require the arrangement of stimuli in sequential order. The Achievement Scale was not used in this study.

The child version of the ANT has been used since 2004, has been validated relative to the adult version, and assesses alerting, orienting, and conflict resolution abilities. Briefly, on a computer screen, children viewed a target (a fish) flanked on each side by 2 distractors above or below a central fixation cross. The target was preceded by 1 of 4 warning cues: a single central asterisk; a double asterisk above and below the fixation point; no asterisk; or a single spatial asterisk located at the same position as the incoming target. Surrounding flankers were incongruent (the central target fish pointed to the side opposite to the flanker fish), congruent (all of the fish pointed to the same side), and neutral (single fish). For each trial, the child was instructed to indicate as quickly as possible whether the central target fish pointed to the left or to the right. Median response times for correct responses and percent errors were reported for each flanker and warning cue condition. Scores were computed by subtracting response times: congruent from incongruent trials (conflict score), double cue from no cue (alerting score), and spatial from central cue (orienting score).

The MoBa study assessed parent-reported child language development and delay at age 3 years with a subset of questions from the MacArthur Communicative Development Inventory: U.K. Short Form grammar scale, which was validated in a subset of the MoBa cohort.[27,28] In the assessment, each mother selected the category that best described the way her child talked: 1) long, complete sentences, 2) fairly complicated sentences, 3) 2-3 word phrases, 4) one-word utterances, 5) talking but unintelligible, 6) not yet talking. At age 3, categories 1 and 2 indicate no language delay, category 3 indicates moderate language delay, and categories 4-6 indicate severe language delay. Handal et al[27] combined moderate and severe delay (categories 4-6) into a single category.

Levine et al[29] identified all children with ASD by linking health care registers from the Meuhedet health care organization that covers 35 percent of Israelis younger than 15 years. After multiple evaluations, children were diagnosed with ASD by a board-recognized developmental behavioral pediatrician. ASD was defined by the ICD-9

codes 299.0, 299.1, or 299.8. Intellectual disability was diagnosed similarly, with additional psychometric cognitive testing and ICD codes for broad psychiatric disorders and intellectual disability.

Evidence synthesis

Generally, across the body of evidence, the association between folic acid supplementation before or during pregnancy and neurobehavioral outcomes were either beneficial or not significant (**Table 21 and Table 22**). There were 4 outcome domains in this body of evidence: social-emotional development,[26] cognitive development,[24,25] language/communication development,[27,28] and autism spectrum disorder,[29] which are discussed in more detail below. Publication bias is a concern with this body of evidence given that there were few studies (particularly within each outcome domain) and all but 1 study reported a significant effect or association of folic acid supplementation. No conclusion statements were drawn for any of the 9 outcome domains listed in the Analytic Framework (**Figure 5**). There was insufficient evidence to draw conclusions related to cognitive development, social-emotional development, language development, and autism spectrum disorder, and no evidence available to draw conclusions for: movement/physical development, academic performance, attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD), anxiety, or depression.

Cognitive development

Summary

Using a 2x2 factorial design, the NUHEAL trial examined the impact of folate (5-MTHF) and fish oil (EPA and DHA) supplementation from 20 weeks gestation through delivery on cognitive development of the offspring. Campoy et al[24] tested the intervention on cognitive development, specifically intelligence, using the K-ABC test when children were 6.5 years old. There was no statistically significant effect of supplementation on children's mental processing (composite score), sequential processing, or simultaneous processing. Catena et al[25] tested children's attention and executive functioning when they were 8.5 years old using the Attention Network Test. Supplementation of folate alone resulted in better conflict scores compared to no supplementation or a combination of fish oil and folate supplementation. There was a statistically significant effect of supplementation on alerting scores such that folate alone and fish oil alone resulted in better alerting scores than the combination of folate and fish oil. There was no statistically significant effect of folate alone compared to the placebo. Other results for correct responses and percent errors were not statistically significant (**Table 21**).

Assessment of the evidence

One study (2 articles) included data on cognitive development and the results were inconsistent, therefore a conclusion statement could not be drawn.[24,25]

Social-emotional development

Summary

Henry et al[26] was the only study to report outcomes in the social-emotional/behavioral

domain and looked specifically at resilience, strengths and difficulties, and emotional intelligence, and compared the effect of folic acid supplementation during the first trimester alone versus supplementation throughout pregnancy. Based on parental report, all traits within the resilience test (creativity, humor, independence, initiative, insight, relationships, values orientation, and total resilience score) showed a significant beneficial association between folic acid supplementation in pregnancy and child resiliency scores. Results from the strengths and difficulties questionnaire (SDQ) and the emotional intelligence questionnaire (TEIQue-CSF) were a mix of either beneficial associations or no association between folic acid supplementation and these traits. From the SDQ, folic acid supplementation was associated with fewer conduct problems, but there were no other statistically significant associations (emotional difficulties, hyperactivity, peer problems, prosocial behavior, and difficulties total). From the TEIQue-CSF, folic acid supplementation was associated with a higher total emotional intelligence score, along with higher scores for emotional expressiveness, empathy, emotional regulation, and stress management. There was no significant association between folic acid supplementation and other emotional intelligence traits (**Table 21**).

Assessment of the evidence

For social-emotional development, a single study met the inclusion criteria.[26] This paper had an analytic sample of 39, with 79 percent attrition from baseline. Further, there were discrepancies in reported results. For example, the paper states that the Trait Emotional Intelligence Questionnaire Child Short Form measures 9 of 15 adult facets of emotional intelligence; however, the paper reported data on all 15 facets. For these reasons, evidence was not strong enough to draw a conclusion statement.

Language development

Summary

Two articles reported results related to language competency in 3-year-old children enrolled in the MoBa cohort. While the population and the outcome assessment were the same in both papers, there was a slight difference in the analyses. Roth et al[28] compared language competency between children whose mothers did not take folic acid supplements during pregnancy and those whose mothers took folic acid from 4 weeks before pregnancy to 8 weeks gestation. There was a statistically significant association between taking folic acid supplements in early pregnancy and fewer children with moderate or severe language delay. Handal et al[27] used folic acid supplementation during early pregnancy as the reference and no folic acid or folic acid later in pregnancy as the comparators and found an association with improved language competence. Children whose mothers took folic acid supplements in early pregnancy, compared to children whose mothers took folic acid in later pregnancy or compared to children whose mothers did not take folic acid supplements at all, were more likely to speak in long, complicated sentences rather than exhibit language delay. The data presented by Handal et al[27] include women who took folic acid along with other micronutrients (hence much larger sample sizes than in the analyses by Roth et al[28]; however, the authors report that the analysis of women who took only folic acid did not change the main results.

Assessment of the evidence

Insufficient data existed to develop conclusion statements regarding language development.[27,28] For the risk of bias assessment (**Table 23**), the papers varied in the key confounders that were accounted for, with Roth et al[28] accounting for all but 2 (race/ethnicity, gestational age) and Handal et al[27] accounting for all but 3 (maternal age, race/ethnicity, human milk feeding practices). Further, exposure data were self-reported with potential for recall bias, there was no information on dose, and neither article pre-registered data analysis plans. Generalizability was limited because data were from 1 study population, from Norway, that does not represent the diversity of the U.S. population.

Autism spectrum disorder

Summary

Levine[29] used a nested case-control design to compare associations between folic acid supplementation before and/or during pregnancy and the risk of an autism diagnosis in children between 8 and 12 years old. Folic acid supplementation before and during pregnancy was associated with a lower risk of autism compared to no folic acid supplementation. Likewise, folic acid before pregnancy only, folic acid during pregnancy only, and folic acid from 4 weeks before pregnancy to 8 weeks after pregnancy were each associated with reduced risk of autism compared to no folic acid supplementation. When folic acid supplementation before pregnancy was compared to folic acid supplementation during pregnancy there was not a significant association with risk of autism. Several subgroup analyses found that, compared to no supplementation, folic acid supplementation before pregnancy and folic acid supplementation during pregnancy were associated with lower risk of autism. These subgroups included: singletons (no siblings), male offspring, female offspring, low socioeconomic status, when neither parent had a psychiatric diagnosis, and in children without intellectual disability. Folic acid supplementation during pregnancy (but not before pregnancy) was significantly associated with lower risk of autism when both parents had a psychiatric diagnosis and in children with intellectual disability.

Assessment of the Evidence

One study included data on autism spectrum disorder, and therefore evidence was not strong enough to draw a conclusion statement.[29] The nested case-control study had serious risk of bias due to confounding, and did not account for race/ethnicity, anthropometry, smoking, gestational age, human milk feeding practices. Classification of the exposure was based on a data registry of supplements dispensed without a measure of actual intake or dosage, and there was risk of bias due to reported selection because no pre-registered analysis plans were reported (**Table 23**). Generalizability was limited because data are from 1 study population from Israel that does not represent the diversity of the U.S. population. Further, high prevalence of psychosis diagnosis in the mothers and fathers limited the generalizability of this evidence.

Table 20. Description of studies examining the relationship between consumption of folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child[xli]

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Randomized Controlled Trials		
Campoy, 2011[24] **RCT (NUHEAL); Germany, Hungary, Spain** **Baseline N=315** **Analytic N=154 (Attrition: 51%)** Power Analysis: Post hoc: 80% power to detect 6.85 (0.7 SD) points of difference in Mental Processing Composite score with a=0.05 **Baseline characteristics:** • Maternal age: Mean~31y • SES: Education: Attained qualification for univ entrance or degree: Mothers: 45%, Fathers: 39.0% • BMI at 20wk: Mean~25.2 • Smokers: 16% • Parity: 0: n=84%, ≥1: n=10% • Child sex, female: 48% • HMF practices (intensity, duration): ○ Fed human milk: 47% ○ Mixed: 16% ○ Formula: 25%	**Exposure:** Maternal intake of folic acid (5-MTHF) and fish oil (FO) supplements in milk-based sachets during 20wk gestation to delivery; 4 groups: • Placebo (Ref, baseline n=80, analytic n=45) • 5-MTHF (400 µg/d, baseline n=77, analytic n=35) • FO (500 mg/d DHA, 150 mg/d EPA, baseline n=77, analytic n=37) • FO+5-MTHF (500 mg/d DHA, 150 mg/d EPA, 400 µg/d 5-MTHF, baseline n=77, analytic n=37) No FA supplementation since beginning of pregnancy; all sachets included vitamins and minerals meeting recommended intakes during the second half of pregnancy for European women. *Exposure assessment method:* Double-blind design; At 20 wk and 30 wk, women provided with 90 sachets, each with 15 g/d of a milk-based supplement. Detailed instructions were given on the label of each sachet. Supplements were indistinguishable with respect to the appearance or	**Confounders accounted for:** • Maternal age, SES, Anthropometry, Smoking Status, Parity, Child sex, GA, HMF practices (intensity, duration) **Not accounted for:** • Key confounders: Race/ethnicity • Other factors considered: Maternal substance use, History/diagnosis of neurocognitive disorders, Complementary feeding **Limitations:** • No preregistered protocol with analysis plan

[xli] ANT: Attention Network Test; ASD: autism spectrum disorder; BMI: body mass index; d: day; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; FA: folic acid; FASSTT: Folic Acid Supplementation in the Second and Third Trimester; FO: fish oil; GA: gestational age; GW: gestational week; HMF: human milk feeding; ICD: International Statistical Classification of Diseases and Related Health Problems; K-ABC: Kaufman Assessment Battery for Children; MoBa: Mother and Child cohort; MTHF: methyltetrahydrofolate; MTHFR: methyltetrahydrofolate reductase; NCC: nested case-control; NICHD: National Institute of Child Health and Human Development; NIEHS: National Institute of Environmental Health Sciences; NIMH: National Institute of Mental Health; NINDS: National Institute of Neurological Disorders and Stroke; NTD: neural tube defect; NUHEAL: Nutraceuticals for a Healthy Life cohort; OR: odds ratio; PCS: prospective cohort study; RASP: Resiliency Attitudes and Skills Profile; RCT: randomized controlled trial; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire; SES: socioeconomic status; TEIQue-CSF: Trait Emotional Intelligence Questionnaire Child Short Form; wk: week(s); y: year(s)

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Center: Spain: n=109 (70.8%), Germany: n=35 (22.7%), Hungary: n=10 (6.5%) • Urban residence: n=63 (40.9%) • Apgar score (1 min): Mean~9, Apgar score (5 min): Mean~10 • GA at birth: Mean~39wk **Funding Sources:** Commission of the European Community–specific Research and Technological Development Programme	contents. Participants instructed to return leftover sachets. Standardized questionnaires assessed adherence at 30wk and at delivery. **Outcome:** • Child intelligence, assessed with the K-ABC at 6.5y *Outcome assessment method:* Child intelligence assessed via the K-ABC at 6.5y. Findings summarized with the Mental Processing Composite, a measure similar to the intelligence quotient, and comprised of the Simultaneous Processing Scale and Sequential Processing Scale. Task Description: The Simultaneous Processing Scale examines problem-solving skills that require processing of many stimuli at once. The Sequential Processing Scale, which primarily measures short-term memory, consists of subtests that evaluate children's ability to solve problems that require the arrangement of stimuli in sequential order. The Achievement scale was not used in this study. Raw scores are transformed into standard scores with Mean=100 (SD=15) and percentile scores.	
Catena, 2016[25] **RCT (NUHEAL); Germany, Hungary, Spain** **Baseline N=315** **Analytic N=130 (Attrition: 58.7%)** **Power Analysis:** Post-hoc: 80% power to detect 36 ms difference in reaction-time conflict score **Baseline characteristics:** • Maternal age: ~31y • SES: Education: Attained qualification level for univ entrance or degree: Mothers: n=56 (43%), Fathers: n=51 (39%), Similar family status,	**Exposure:** Maternal intake of folic acid (5-MTHF) and fish oil (FO) supplements in milk-based sachets during 20wk gestation to delivery; 4 groups: • Placebo (Ref, baseline n=80, analytic n=32) • 5-MTHF (400 µg/d, baseline n=77, analytic n=27) • FO (500 mg/d DHA, 150 mg/d EPA, baseline n=77, analytic n=37) • FO+5-MTHF (500 mg/d DHA, 150 mg/d EPA, 400 µg/d 5-MTHF, baseline n=77, analytic n=34) No FA supplementation since beginning of pregnancy; all sachets included vitamins and minerals meeting recommended intakes during the second half of pregnancy for European women.	**Confounders accounted for:** • Maternal age, SES, Anthropometry, Smoking Status, Parity, Child sex, GA, HMF practices (intensity, duration) **Not accounted for:** • Key confounders: Race/ethnicity • Other factors considered: Maternal substance use, History/diagnosis of neurocognitive disorders, Complementary feeding **Limitations:** No preregistered protocol with analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
including mother's and father's jobs, employment, career, cultural, and academic levels • Prepregnancy BMI: Mean~25 at 20GW • Smokers: n=16 (12%) • Parity: 0: n=62 (48%), ≥1: n=68 (52%) • Child sex: Female: n=63 (48%) • HMF practices (intensity, duration): ○ Fed human milk: n=53 (41%) ○ Mixed: n=26 (20%) ○ Formula: n=29 (22%) • MTHFR status: MTHFR C677T polymorphisms distributed similar between groups • Center: Spain: n=91 (70%), Germany: n=32 (25%), Hungary: n=7 (5%) • Urban residence: n=52 (40%) • Apgar score (1 min): Mean ~8.7, Apgar score (5 min): Mean~9.7 • GA at birth: Mean~39.4wk **Funding Sources:** Commission of the European Research and Technological Development Programme, Spanish Ministry of Economy and Competitiveness, European Research Council	*Exposure assessment method:* Double-blind design; At 20wk and 30 wk, women provided with 90 sachets, each with 15 g/d of a milk-based supplement. Detailed instructions were given on the label of each sachet. Supplements were indistinguishable with respect to the appearance or contents. Participants instructed to return leftover sachets. Standardized questionnaires assessed adherence at 30wk and at delivery. **Outcome:** • Child attention network development, assessed with Alerting, Orienting, and Conflict scores and % errors from the ANT at 8.5y *Outcome assessment method:* At 8.5y, children of supplemented mothers completed the ANT, child version. Electroencephalography collected simultaneously. Median RTs for correct responses and % errors obtained for each flanker and warning cue condition. Scores computed by subtracting RTs: congruent from incongruent trials (conflict score), double cue from no cue (alerting score), and spatial from central cue (orienting score).	
Henry, 2018[26] **RCT (FASSTT); United Kingdom** **Baseline N=190** **Analytic N=39 (Attrition: 79%)** **Power Analysis**: n=60 per group at 80% power with a=0.05 to detect a difference in homocysteine concentration in maternal plasma at 36 wk gestation and cord blood at delivery of 0.5 mmol/L between placebo and treatment groups. **Baseline characteristics:**	**Exposure:** Maternal intake of 400 µg/d folic acid supplements during 14wk gestation to delivery; 2 groups: • Placebo (Ref; baseline n=94, analytic n=17) • 400 µg/d FA (baseline n=96, analytic n=22) All women consumed 400 µg/d folic acid for the first trimester *Exposure assessment method:* Supplements were distributed every 4wk to the participant's home in 7-d pillboxes with instructions to take one tablet each morning. The pillboxes were	**Confounders accounted for:** • Maternal age, Race/ethnicity, SES, Anthropometry, Smoking Status, Child sex, HMF practices (intensity, duration) **Not accounted for:** • Key confounders: Parity,GA • Other factors considered: History/diagnosis of neurocognitive disorders, Complementary feeding **Limitations:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
• Maternal age: Median~28y • Children: Mean=6.7y (range 6.3-7.3y) • Race/Ethnicity: Mothers: White: 100% • SES: ○ Education: ~16y ○ Homeowner: 77% • Prepregnancy BMI: ~25 • Smoking status: ~13% • Parity: ~0.95 • Child sex, female: ~64% • HMF practices (intensity, duration): Fed human milk from birth: ~46% • Substance use: Alcohol: ~5% • Family history/diagnosis of neurocognitive disorders: 0% NT sufferer or 1st degree relative of woman with a pregnancy with an NTD • MTHFR status: CC: ~41%; CT: ~44%; TT: ~14% • Maternal serum folate at birth (median; nmol/L): Placebo 72.15, 400 µg/d FA 119.49 **Funding Sources:** The Health and Social Care Research & Development Division of the Public Health Agency, Northern Ireland	collected, and the number of unused tablets was recorded to monitor adherence. **Outcome:** • Strengths and difficulties; Resiliency; Emotional Intelligence at 7y *Outcome assessment method:* Resiliency assessed via maternal report with the RASP; Strengths and difficulties assessed via maternal report with the SDQ; Emotional intelligence was assessed via maternal report with the TEIQue-CSF.	• Some concerns about missing outcome data in this follow-up study • No preregistered protocol with analysis plan
Cohort Studies		
Handal, 2016[27] **PCS (MoBa); Norway** **Baseline N=45266 mothers; 51747 children** **Analytic N=43322; 51375 children (Attrition: 4%)** **Baseline characteristics:** • Maternal age: <25y: ~9.0%, 25-29y: ~33.4%, 30-34y: ~39.8%, ≥35y: ~17.8% • SES: ○ Mother Education: <12y ~16.8%, 12y ~14.4%, 13-16y ~43.9%, ≥17y ~24.9%	**Exposure:** Maternal intake of folic acid supplements; 3 groups: • No folic acid supplementation (analytic n=7330) • FA during early pregnancy (Ref, 4wk before conception through 8wk gestation, analytic n=37538) • FA later in pregnancy (9-29wk gestation only, analytic n=6507) *Exposure assessment method:* Completed questionnaires at 17/18wk and 30wk gestation, indicating intervals of folic acid	**Confounders accounted for:** • SES, Anthropometry, Smoking Status, Parity, Child sex, GA **Not accounted for:** • Key confounders: Maternal age, Race/ethnicity, HMF practices (intensity, duration) • Other factors considered: Maternal substance use, Complementary feeding **Limitations:**

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
○ Father Education: <12y ~33.8%, 12y ~12.9%, 13-16y ~29.2%, ≥17y ~24.2% ○ Mother marital status: Married or living with partner ~97.4%, Single ~1.7%, Other ~0.9% ○ Mother working status: Working ~92.4%, Not working ~5.6%, Disability pensioner ~0.7%, Other ~1.3% • Prepregnancy BMI: early pregnancy: <25 ~69.6%, 25-29 ~21.5%, 30-34 ~6.6%, ≥35 ~2.3% • Smokers: ~7.7% • Parity: 0 ~47.7%, 1 ~34.3%, ≥2 ~18.0% • Substance use: ○ Maternal alcohol intake during pregnancy: Yes (probably occasionally) ~46.6%, Weekly ~3.8% ○ Maternal illicit drug use during pregnancy: ~0.2% • Family history/diagnosis of neurocognitive disorders: ○ Maternal depression before pregnancy: ~5.2% ○ Maternal anxiety and depression during pregnancy: Short-term: ~6.1%, Long-term: ~2.1% ○ Maternal antipsychotic use: ~0.8%, Paternal antipsychotic use: ~0.2% **Funding Sources:** The Norwegian Institute of Public Health, the South-Eastern Norway Regional Health Authority, the Norwegian Ministry of Health and the Ministry of Education and Research, NIEHS, NINDS, the Norwegian Research Council	supplementation, including 4wk before conception, and at 0-4, 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, and ≥29 wk gestation. **Outcome:** • Language competence at age 3y *Outcome assessment method:* Mothers selected the category that best described the way her child talked: 1) long, complete sentences, 2) fairly complicated sentences, 3) 2-3 word phrases, 4) one-word utterances, 5) talking but unintelligible, 6) not yet talking. The 3 outcome categories thus were: long, complicated sentences (category 1), fairly complicated sentences (category 2), and language delay (categories 3–6). Language delay category combines moderate and severe delay.	• Exposure data are self-report; dose NR • No preregistered protocol with analysis plan • Power analysis NR
Roth, 2011[28] **PCS (MoBa); Norway** **Baseline N=16814** **Analytic N=16179 (Attrition: 3%)** **Power Analysis**: n=30000 at 90% power with a=0.05 to detect OR=0.5 in risk of severe language delay at 3y between children unexposed and exposed to maternal use of folic acid (4 groups)	**Exposure:** Maternal intake of folic acid supplements during the periconceptional period (4wk before to 8wk after conception); 2 groups: • No supp (Ref, n=9460, analytic n=9032) • FA (n=7354, analytic n=7127) *Exposure assessment method:*	**Confounders accounted for:** • Maternal age, SES, Anthropometry, Smoking Status, Parity, Child sex, HMF practices (intensity, duration) **Not accounted for:** • Key confounders: Race/ethnicity, GA

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Baseline characteristics: • Maternal age: <25y ~11.0%, 25-29y ~34.2%, 30-34y ~38.5%, ≥35y ~16.4% • SES: ○ Maternal education: <12y ~21.4%, No supp: 26.5%, FA: 16.2%, 12y ~13.9%, No supp: 15.7%, FA: 12.0%, 13-16y ~42.7%, No supp: 38.8%, FA: 46.6%, ≥17y ~19.6%, No supp: 16.1%, FA: 23.0%; ○ Maternal marital status: Married or living with partner 92.2%, Single 3.3%, Other 1.9%; ○ Paternal education: <12y ~37.8%, No supp: 42.3%, FA: 33.3%, 12y ~10.7%, 13-16y ~25.1%, ≥17y ~17.3%, Missing ~7.0% • Prepregnancy BMI: <25 ~63.8%, 25-29 ~23.2%, 30-34 ~7.6%, ≥35 ~2.7% • Smoking status: Daily or sometimes: ~9.3% ○ No supp: 12.3%, FA: 6.2% • Parity: 0 ~43.1%, 1 ~37.1%, ≥2 ~19.9% • Child sex: Male: ~51.2%, Female: ~48.8% • HMF practices (intensity, duration): Type of milk at 6mo: ○ Breast milk ~56.0% ○ Infant formula ~14.2% ○ Breast milk and infant formula ~19.4% ○ Missing ~10.5% • Substance use: Maternal alcohol intake: ~12.5%, Missing ~9.6% **Funding Sources:** The Norwegian Ministry of Health and the Ministry of Education and Research, NIEHS, NINDS, The Norwegian Research Council, National Alliance for Research on Schizophrenia and Depression, The Norwegian Research Council, The American Women's Club of Oslo	Completed questionnaires at 17wk gestation, indicating intervals of folic acid supplementation, including 4wk before conception, and at 0-4, 5-8wk gestation. Women recorded ingredient list for all vitamins, minerals, and other dietary supplements during each period. Responses divided into mutually exclusive categories of use within 4wk before to 8wk after conception: 1) no use of dietary supplements; and (2) folic acid only. **Outcome:** • Severe or moderate language delay at 3 y *Outcome assessment method:* Mothers selected the category that best described the way her child talked: 1) long, complete sentences, 2) fairly complicated sentences, 3) 2-3 word phrases, 4) one-word utterances, 5) talking but unintelligible, 6) not yet talking. The 3 outcome categories thus were: No language delay (categories 1 and 2), Moderate language delay (category 3), and Severe language delay (categories 4-5). Category 6 assessed, but excluded (n=63) for chromosomal abnormalities or severe syndromes. A subsample (n=425) administered in-depth assessments within the MoBa cohort at 3y. Scores from the present study were strongly correlated with the Vineland communication domain, a semistructured interview administered by clinicians who were blind to the maternal reports. The communication domain evaluates the child's receptive and expressive communication skills.	• Other factors considered: History/diagnosis of neurocognitive disorders, Complementary feeding **Limitations:** • Exposure data are self-report; dose NR • No preregistered protocol with analysis plan
Nested Case-Control Study		

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
Levine, 2018[29] **NCC; Israel** **Baseline N=45300** **Analytic N=45300 (Attrition: 0%)** **Baseline characteristics:** • Maternal age: ≥35y: Controls: n=8975 (20.1%), Cases: n=118 (20.6%) • SES: ○ Low: n=27,383 (60.4%), Controls: n=27,140 (60.7%), Cases: n=243 (42.5%); ○ High: n=17,917 (39.6%), Controls: 17,588 (39.3%), Cases: 329 (57.5%) • Parity: ○ 1: n=11,419 (25.2%), Controls: n=11,150 (24.9%), Cases: n=269 (47.0%) ○ >1 child: n=33,881 (74.8%), Controls: n=33,578 (75.1%), Cases: n=303 (53.0%) • Child sex: Female: n= 22090 (48.8%), Controls: n=21988 (49.2%), Cases: n=102 (17.8%) • Family history/diagnosis of neurocognitive disorders: ○ Paternal psychiatric diagnosis: n= 15177 (33.5%), Controls: n=14,919 (33.4%), Cases: n=258 (45.1%) ○ Maternal psychiatric diagnosis: n=15098 (33.3%), Controls: n=14,869 (33.2%), Cases: n=229 (40.0%) **Funding Sources:** NICHD, NIEHS, NINDS, NIMH, Beatrice and Samuel A. Seaver Foundation, Fredrik and Ingrid Thuring Foundation, and The Swedish Society of Medicine	**Exposure:** Maternal folic acid supplementation; 4 groups: • No FA supp (n=26,332) • FA supp before pregnancy only (271-540d before delivery, n=3085) • FA supp during pregnancy only (0-270d before delivery, n=11,741) • FA supp before and during pregnancy only (0-540d before delivery, n=4142) *Exposure assessment method:* Meuhedet Prescription Register used to identify prescription folic acid supplement dispensation from the majority of pharmacies nationwide during pregnancy. Using ATC codes, authors extracted drug names, prescription and dispensation dates, and number of pills dispensed, for redeemed folic acid supplements. Israeli food supply not fortified with folic acid, but folic acid supplementation is recommended before and during pregnancy. **Outcome:** • ASD diagnosis, with and without comorbid intellectual disability in children 8-12y *Outcome assessment method:* Identified all children with ASD and one-third of all live births Jan 1, 2003, to Dec 31, 2007, followed from birth to Jan 26, 2015. Cases identified by linking health care registers from the Meuhedet health care organization that covers 35% of Israelis <15y. After multiple evaluations, children diagnosed with ASD by a board-recognized developmental behavioral pediatrician. ASD defined by the ICD-9 codes 299.0, 299.1, or 299.8. Intellectual disability diagnosed similarly, with additional psychometric cognitive testing and ICD	**Confounders accounted for:** • Maternal age, SES, Parity, Child sex **Not accounted for:** • Key confounders: Race/ethnicity, Anthropometry, Smoking, GA, HMF practices (intensity, duration) • Other factors considered: Maternal substance use, Complementary feeding **Limitations:** • Exposure based on data on supplements dispensed, not on intake • Power analysis NR • No pre-registered analysis plan

Study and Population Characteristics	Intervention/Exposure and Outcome(s)	Confounders Accounted for and Study Limitations
	codes for broad psychiatric disorders and intellectual disability.	

Table 21. Results from studies that examined the relationship between consumption of folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child[xlii, xliii]

Article	Intervention/Exposure	Outcome and Results
Randomized Controlled Trials		
Campoy, 2011[24] **RCT; Germany,Hungary,Spain** **Summary:** Consuming 400 µg/d folic acid supplements with or without fish oil during the second half of pregnancy did not impact child intelligence as measured by the K-ABC at 6.5y. **Limitations:** • Key confounders NOT accounted for: Race/ethnicity • No preregistered protocol with analysis plan	Maternal intake of folic acid (5-MTHF) and fish oil (FO) supplements in milk-based sachets from 20wk gestation to delivery; 4 groups: • Placebo (Ref, baseline n=80, analytic n=45), • 5-MTHF (400 µg/d, baseline n=77, analytic n=35), • FO (500 mg/d DHA, 150 mg/d EPA, baseline n=77, analytic n=37), • FO+5-MTHF (500 mg/d DHA, 150 mg/d EPA, 400 µg/d 5-MTHF, baseline n=77, analytic n=37) No FA supplementation since beginning of pregnancy; all sachets included vitamins and minerals meeting recommended intakes during the second half of pregnancy for European women.	**Kaufman Assessment Battery for Children (K-ABC)** **Mental Processing Composite** (Median (IQR)), Kruskal-Wallis, P=0.82 • Placebo: 110 (14.5) • 5-MTHF: 108 (12.0) • FO: 110 (11.0) • FO + 5-MTHF: 108 (10.5) **Sequential Processing Scale** (Median (IQR)), Kruskal-Wallis, P=0.57 • Placebo: 106 (19) • 5-MTHF: 104 (14) • FO: 108 (12) • FO + 5-MTHF: 104 (17) **Simultaneous Processing Scale** (Median (IQR)), Kruskal-Wallis, P=0.88 • Placebo: 112 (11.5) • 5-MTHF: 109 (14) • FO: 112 (10.5) • FO + 5-MTHF: 110 (10.5)
Catena, 2016[25] **RCT; Germany,Hungary,Spain** **Summary:**	Maternal intake of folic acid (5-MTHF) and fish oil (FO) supplements in milk-based sachets during 20wk gestation to delivery; 4 groups:	**ANT: Correct responses:** **Global Speed Response Times** for correct responses (Median ± SD, ms), ANCOVA of log-transformed means, P=0.07

[xlii] ANCOVA: analysis of covariance; ANT: Attention Network Test; ASD: autism spectrum disorder; CI: confidence interval; d: day; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; FA: folic acid; FO: fish oil; IQR: interquartile range; K-ABC: Kaufman Assessment Battery for Children; MTHF: methyltetrahydrofolate; NCC: nested case-control; OR: odds ratio; PCS: prospective cohort study; RASP: Resiliency Attitudes and Skills Profile; RCT: randomized controlled trial; RR: relative risk; RRR: relative risk ratio; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire; SES: socioeconomic status; TEIQue-CSF: Trait Emotional Intelligence Questionnaire Child Short Form; wk: week(s); y: year(s)

[xliii] Statistically significant findings bolded

Article	Intervention/Exposure	Outcome and Results
Consuming 400 µg/d folic acid supplements during the second half of pregnancy improved conflict response times on the ANT at 8.5y versus placebo, but did not effect response speed or accuracy for altering or orienting. Consuming 400 µg/d folic acid plus fish oil compared to fish oil alone or 5-MTHF alone during the second half of pregnancy worsened the alerting response. **Limitations:** • Key confounders NOT accounted for: Race/ethnicity • No preregistered protocol with analysis plan	• Placebo (Ref, baseline n=80, analytic n=32), • 5-MTHF (400 µg/d, baseline n=77, analytic n=27), • FO (500 mg/d DHA, 150 mg/d EPA, baseline n=77, analytic n=37), • FO+5-MTHF (500 mg/d DHA, 150 mg/d EPA, 400 µg/d 5-MTHF, baseline n=77, analytic n=34) No FA supplementation since beginning of pregnancy; all sachets included vitamins and minerals meeting recommended intakes during the second half of pregnancy for European women.	• Placebo: 818 ± 132 • 5-MTHF: 872 ± 98 • FO: 854 ± 135 • FO + 5-MTHF: 825 ± 111 **Conflict Score** (Interference; Incongruent minus Congruent, Lower=more efficient executive network; Median ± SD, ms), ANCOVA of log-transformed means, P=0.01 • Placebo: 101 ± 63 • 5-MTHF: 60 ± 75 • FO: 83 ± 67 • FO + 5-MTHF: 96 ± 66 MTHF, P<0.01 • Simple effects: **5-MTHF < Placebo, P<0.05**; 5-MTHF < FO+5-MTHF, P<0.05; 5-MTHF = FO • Interactions: flanker*FO*5- ○ , P=0.24 **Orienting Score** (Central minus Spatial cue, Lower=more efficient orienting network; Median ± SD, ms), ANCOVA of log-transformed means, P=0.95 • Placebo: 41 ± 54 • 5-MTHF: 36 ± 69 • FO: 47 ± 48 • FO + 5-MTHF: 38 ± 70 • Interactions: FO*5-MTHF, NS **Alerting Score** (No cue minus Double cue, Lower=more efficient alerting network; Median ± SD, ms), ANCOVA of log-transformed means, P=0.03 • Placebo: 74 ± 65 • 5-MTHF: 48 ± 77 • FO: 43 ± 56 • FO + 5-MTHF: 71 ± 55 • Interactions: FO*5-MTHF, P<0.03 ○ Simple effects: **FO < FO+5-MTHF, P<0.04**; 5-MTHF < FO+5-MTHF, P<0.04

Article	Intervention/Exposure	Outcome and Results
		ANT: Percent errors: **Total % errors** (Mean ± SD), ANCOVA, P=0.42 • Placebo: 7.2 ± 6.2 • 5-MTHF: 8.0 ± 7.3 • FO: 8.1 ± 5.8 • FO + 5-MTHF: 6.9 ± 6.1 **Conflict % error** (Incongruent cue minus Congruent cue, Mean ± SD), ANCOVA, P=0.52 • Placebo: 6.3 ± 10.8 • 5-MTHF: 4.8 ± 6.4 • FO: 4.0 ± 5.3 • FO + 5-MTHF: 5.8 ± 8.0 **Orienting % error** (Central cue minus Spatial cue, Mean ± SD), ANCOVA, P=0.81 • Placebo: -0.3 ± 5.7 • 5-MTHF: -0.3 ± 7.3 • FO: 0.3 ± 6.0 • FO + 5-MTHF: -0.2 ± 5.0 **Alerting % error** (No cue minus Double cue, Mean ± SD), ANCOVA, P=0.32 • Placebo: -0.1 ± 5.5 • 5-MTHF: 1.2 ± 4.1 • FO: 1.2 ± 6.9 • FO + 5-MTHF: 0.5 ± 6.1
Henry, 2018[26] **RCT; United Kingdom** **Summary:** Consuming 400 µg/d folic acid supplements throughout pregnancy resulted in improved resilience and emotional intelligence in children at 7y compared to children whose mothers consumed 400 µg/d folic acid in the first trimester alone. There was no effect of	Maternal intake of 400 µg/d folic acid supplements during 14wk gestation to delivery; 2 groups: • Placebo (Ref, baseline n=94, analytic n=17) • 400 µg/d FA (baseline n=96, analytic n=22) All women consumed 400 µg/d folic acid for the first trimester	**RASP (Higher scores=more resilience)** **Resilience total**, Mann–Whitney, P=0.001 • Placebo: Median=3.75, IQR=0.36 • **FA: Median=4.18, IQR=0.31** **Creativity**, Mann–Whitney, P=0.008 • Placebo: Median=3.75, IQR=0.63 • **FA: Median=4.25, IQR=0.56** **Humour**, Mann–Whitney, P=0.003

Article	Intervention/Exposure	Outcome and Results
maternal folic acid supplementation during the second and third trimester on child difficulties or pro-social behavior. **Limitations:** • Key confounders NOT accounted for: Parity,Gestational age • Some concerns about missing outcome data in this follow-up study • No preregistered protocol with analysis plan		• Placebo: Median=3.25, IQR=1.13 • **FA: Median=3.88, IQR=1.00** **Independence**, Mann–Whitney, P=0.001 • Placebo: Median=3.63, IQR=0.69 • **FA: Median=4.00, IQR=0.75** **Initiative**, Mann–Whitney, P=0.017 • Placebo: Median=3.60, IQR=0.80 • **FA: Median=4.00, IQR=0.60** **Insight**, Mann–Whitney, P=0.006 • Placebo: Median=3.86, IQR=0.57 • **FA: Median=4.29, IQR=0.64** **Relationships**, Mann–Whitney, P=0.003 • Placebo: Median=4.00, IQR=0.44 • **FA: Median=4.50, IQR=0.53** **Values orientation**, Mann–Whitney, P=0.007 • Placebo: Median=4.00, IQR=0.63 • **FA: Median=4.38, IQR=0.56** **SDQ (Lower scores=fewer difficulties)** **Difficulties total**, Mann–Whitney, P=0.217 • Placebo: Median=11.00, IQR= 12.50 • FA: Median=6.00, IQR=4.25 **Emotional difficulties**, Mann–Whitney, P=0.863 • Placebo: Median=3.00, IQR=7.00 • FA: Median=2.50, IQR=4.25 **Conduct problems**, Mann–Whitney, P=0.038 • Placebo: Median=3.00, IQR=3.50 • **FA: Median=0.50, IQR=7.00** **Hyperactivity**, Mann–Whitney, P=0.455 • Placebo: Median=4.00, IQR=7.00

Article	Intervention/Exposure	Outcome and Results
		• FA: Median=3.00, IQR=4.50 **Peer problems**, Mann–Whitney, P=0.884 • Placebo: Median=1.00, IQR=5.00 • FA: Median=1.00, IQR=2.00 **Prosocial behaviour (Higher scores=beneficial)**, Mann–Whitney, P=0.426 • Placebo: Median=9.00, IQR=4.00 • FA: Median=10.00, IQR=1.00 **TEIQue-CSF (Higher scores=beneficial)** **Emotional Intelligence total**, Mann–Whitney, P=0.001 • Placebo: Median=57.00, IQR=7.00 • **FA: Median=64.50, IQR=8.50** **Emotional expressive**, Mann–Whitney, P=0.006 • Placebo: Median=4.00, IQR=0.50 • **FA: Median=4.50, IQR=1.00** **Empathy**, Mann–Whitney, P=0.026 • Placebo: Median=3.00, IQR=1.00 • **FA: Median=4.00, IQR=1.25** **Self-motivation**, Mann–Whitney, P=0.154 • Placebo: Median=4.00, IQR=2.00 • FA: Median=4.00, IQR=1.00 **Emotional regulation**, Mann–Whitney, P=0.038 • Placebo: Median=3.00, IQR=2.00 • **FA: Median=4.00, IQR=1.25** **Happiness**, Mann–Whitney, P=0.056 • Placebo: Median=4.00, IQR=1.00 • FA: Median=5.00, IQR=1.00 **Social awareness**, Mann–Whitney, P=0.076 • Placebo: Median=4.00, IQR=1.00

Article	Intervention/Exposure	Outcome and Results
		• FA: Median=5.00, IQR=1.00 **Low impulsivity**, Mann–Whitney, P=0.098 • Placebo: Median=4.00, IQR=1.00 • FA: Median=4.00, IQR=3.00 **Emotional perceptive**, Mann–Whitney, P=0.467 • Placebo: Median=4.00, IQR=2.00 • FA: Median=4.00, IQR=0.25 **Self esteem**, Mann–Whitney, P=0.082 • Placebo: Median=4.00, IQR=1.00 • FA: Median=4.50, IQR=1.00 **Assertiveness**, Mann–Whitney, P=0.123 • Placebo: Median=4.00, IQR=1.00 • FA: Median=4.00, IQR=0.25 **Emotion management**, Mann–Whitney, P=0.346 • Placebo: Median=4.00, IQR=0.50 • FA: Median=4.00, IQR=0.25 **Optimism**, Mann–Whitney, P=0.309 • Placebo: Median=4.00, IQR=0.25 • FA: Median=4.00, IQR=0.25 **Relationships**, Mann–Whitney, P=0.076 • Placebo: Median=4.00, IQR=1.00 • FA: Median=5.00, IQR=1.00 **Adaptable**, Mann–Whitney, P=0.026 • Placebo: Median=4.00, IQR=1.00 • FA: Median=4.00, IQR=1.00 **Stress management**, Mann–Whitney, P=0.030 • Placebo: Median=3.00, IQR=1.00 • **FA: Median=4.00, IQR=0.50**

Article	Intervention/Exposure	Outcome and Results
Cohort Studies		
Handal, 2016[27] **PCS; Norway** **Summary:** Compared to consuming folic acid during early pregnancy (4 weeks before to 8 weeks pregnant), not consuming folic acid and consuming folic acid in later pregnancy (9 to 29 weeks gestation) was positively associated with language competence when the child was 3y (child's language delay vs ability to speak in long complicated sentences) but not statistically associated with the child's ability to speak in fairly completely sentences versus long, complicated sentences. **Limitations:** • Key confounders NOT accounted for: Maternal age, Race/ethnicity, Human milk feeding practices (intensity, duration) • Exposure data are self-report; dose NR • No preregistered protocol with analysis plan • Power analysis NR	Maternal intake of folic acid supplements; 3 groups: • No folic acid supplementation (analytic n=7330) • FA during early pregnancy (Ref; 4wk before conception through 8wk gestation, analytic n=37538) • FA later in pregnancy (9-29wk gestation only, analytic n=6507)	**Language Competence*** **Fairly complete sentences vs long, complicated sentences**, Multinomial logistic regression (Adj RRR (95% CI), n=49687) • FA during -4 through 8wk gestation (n=36250): Ref • FA during 9 through 29wk gestation (n=6188): 1.1 (1.0, 1.2) • No FA (n=6899): 1.1 (1.0, 1.2) **Language delay vs long, complicated sentences**, Multinomial logistic regression (Adj RRR (CI), n=41900) • FA during -4 through 8wk gestation (n=30790): Ref • **FA during 9 through 29wk gestation (n=5172): 1.2 (1.1, 1.4)** • **No FA (n=5644): 1.3 (1.1, 1.5)** * Data include women who took FA with other vits/minerals, but "the main results did not change with the alternative analytical approaches, excluding mothers who used multivitamins during pregnancy"
Roth, 2011[28] **PCS; Norway** **Summary:** Consuming folic acid supplements during the periconceptional period (4wk before to 8wk after conception) was associated with a reduced risk of moderate and	Maternal intake of folic acid supplements during the periconceptional period (4wk before to 8wk after conception); 2 groups: • No supp (Ref, n=9460, analytic n=9032) • FA only (n=7354, analytic n=7127)	**Language Competence** **Severe language delay**, Logistic regression • No Supp (Ref): n=81 (0.9%) • FA: n=28 (0.4%) • **Adjusted OR=0.55, 95% CI: 0.35, 0.86** **Severe language delay among males** (n=8146), Logistic regression • No Supp (Ref): n=62 (1.4%)

Article	Intervention/Exposure	Outcome and Results
severe language delay in children at 3y compared with no dietary supplements. **Limitations:** • Key confounders NOT accounted for: Race/ethnicity, Gestational age • Exposure data are self-report; dose NR • No preregistered protocol with analysis plan		• FA: n=24 (0.7%) • Adjusted OR=0.61, 95% CI: 0.37, 1.00 **Severe language delay among females** (n=8033), Logistic regression • No Supp (Ref): n=19 (0.4%) • FA: n=4 (0.1%) • Adjusted OR=0.36, 95% CI: 0.12, 1.10 **Moderate language delay**, Logistic regression • No Supp (Ref): n=404 (4.4%) • FA: n=227 (3.1%) • **Adjusted OR=0.82, 95% CI: 0.69, 0.97**
Nested Case-Control Studies		
Levine, 2018 [29] **NCC; Israel** **Summary:** Consuming folic acid supplements before and/or during pregnancy was associated with a reduced risk of ASD in the children compared with the children of mothers without such exposure. **Limitations:** • Key confounders NOT accounted for: Race/ethnicity, Anthropometry, Smoking, Gestational age, Human milk feeding practices (intensity, duration) • Exposure based on data on supplements dispensed, not on intake • No pre-registered analysis plan • Power analysis NR	Maternal folic acid supplementation; 4 groups: • No FA supp (n=26332) • FA supp before pregnancy only (271-540d before delivery, n=3085) • FA supp during pregnancy only (0-270d before delivery, n=11741) • FA supp before and during pregnancy only (0-540d before delivery, n=4142)	**Risk of ASD**, Adjusted Cox proportional hazards regression: **FA before and during pregnancy**: **RR=0.35, 95% CI: 0.24, 0.50; P<0.001** • Cases: exposed=29, not exposed=469 • Controls: exposed=4113, not exposed=25863 **FA before pregnancy only**: **RR=0.31, 95% CI: 0.19, 0.48; P<0.001** • Cases: exposed=19, not exposed=469 • Controls: exposed=3066, not exposed=25863 **FA during pregnancy only**: **RR=0.25, 95% CI: 0.19, 0.33; P<0.001** • Cases: exposed=55, not exposed=469 • Controls: exposed=11686, not exposed=25863 **FA before vs during pregnancy**: RR=0.84, 95% CI: 0.50, 1.42; P=0.52 • Cases: exposed before pregnancy only=19, exposed during pregnancy only=55 • Controls: exposed before pregnancy only=3066, exposed during pregnancy only=11686

Article	Intervention/Exposure	Outcome and Results
		FA from 4wk preconception to 8wk postconception: **RR=0.41, 95% CI: 0.31, 0.55; P<0.001** • Cases: exposed=50, not exposed=522 • Controls: exposed=8111, not exposed=36617 **Sub-analysis among singletons (no siblings)** **FA before pregnancy**: **RR=0.53, 95% CI: 0.35, 0.79; P=0.002** • Cases: exposed=24, not exposed=245 • Controls: exposed=1865, not exposed=9285 **FA during pregnancy**: **RR=0.37, 95% CI: 0.27, 0.50; P<0.001** • Cases: exposed=46, not exposed=223 • Controls: exposed=4082, not exposed=7068 **Sub-analysis among male offspring** **FA before pregnancy**: **RR=0.57, 95% CI: 0.42, 0.79; P<0.001** • Cases: exposed=40, not exposed=430 • Controls: exposed=3642, not exposed=19098 **FA during pregnancy**: **RR=0.33, 95% CI: 0.26, 0.43; P<0.001** • Cases: exposed=70, not exposed=400 • Controls: exposed=7997, not exposed=14743 **Sub-analysis among female offspring** **FA before pregnancy**: **RR=0.49, 95% CI: 0.24, 0.99; P=0.05** • Cases: exposed=8, not exposed=94 • Controls: exposed=3537, not exposed=18451 **FA during pregnancy**: **RR=0.28, 95% CI: 0.16, 0.49; P<0.001** • Cases: exposed=14, not exposed=88 • Controls: exposed=7802, not exposed=14186 **Sub-analysis among low SES group** **FA before pregnancy**: **RR=0.46, 95% CI: 0.27, 0.81; P=0.006** • Cases: exposed=13, not exposed=230 • Controls: exposed=3899, not exposed=23241 **FA during pregnancy**: **RR=0.23, 95% CI: 0.15, 0.35; P<0.001**

Article	Intervention/Exposure	Outcome and Results
		• Cases: exposed=25, not exposed=218 • Controls: exposed=9332, not exposed=17808 **<u>Sub-analysis among both parents with psychiatric diagnosis</u>** **FA before pregnancy**: RR=0.75, 95% CI: 0.44, 1.28; P=0.29 • Cases: exposed=15, not exposed=111 • Controls: exposed=1090, not exposed=5063 **FA during pregnancy**: **RR=0.30, 95% CI: 0.19, 0.48; P<0.001** • Cases: exposed=19, not exposed=107 • Controls: exposed=2334, not exposed=3819 **<u>Sub-analysis among both parents without psychiatric diagnosis</u>** **FA before pregnancy: RR=0.50, 95% CI: 0.29, 0.84; P=0.009** • Cases: exposed=14, not exposed=197 • Controls: exposed=3192, not exposed=17901 **FA during pregnancy: RR=0.34, 95% CI: 0.23, 0.50; P<0.001** • Cases: exposed=29, not exposed=182 • Controls: exposed=7085, not exposed=14008 **<u>Sub-analysis among children with intellectual disability diagnosis</u>** **FA before pregnancy**: RR=0.66, 95% CI: 0.25, 1.76; P=0.41 • Cases: exposed=44, not exposed=474 • Controls: exposed=7183, not exposed=37599 **FA during pregnancy**: **RR= 0.12, 95% CI: 0.04, 0.36; P<0.001** • Cases: exposed=81, not exposed=437 • Controls: exposed=15802, not exposed=28980 **<u>Sub-analysis among children without intellectual disability diagnosis</u>** **FA before pregnancy**: **RR= 0.55, 95% CI: 0.40, 0.74; P<0.001** • Cases: exposed=4, not exposed=50 • Controls: exposed=7223, not exposed=38023 **FA during pregnancy**: **RR=0.35, 95% CI: 0.28, 0.44; P<0.001**

Article	Intervention/Exposure	Outcome and Results
		• Cases: exposed=3, not exposed=51 • Controls: exposed=15880, not exposed=29366

Table 22. Risk of bias for randomized controlled trials examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child[xliv, xlv]

	Randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Henry, 2018[26]	Low	Low	Some concerns	Low	Some concerns
Catena, 2016[25]	Low	Low	Low	Low	Some concerns
Campoy, 2011[24]	Low	Low	Low	Low	Some concerns

[xliv] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[xlv] Possible ratings of low, some concerns, or high determined using the "Cochrane Risk-of-bias 2.0" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

Table 23. Risk of bias for observational studies examining folic acid from dietary supplements and/or fortified foods during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child[xlvi]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Handal, 2016[27]	Serious	Low	Moderate	Low	Low	Low	Moderate
Roth, 2011[28]	Serious	Low	Moderate	Low	Low	Low	Moderate
Levine, 2018[29]	Serious	Low	Moderate	Low	Low	Low	Moderate

[xlvi] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

Research recommendations

More research is needed:

- To assess the relationship between folate from fortified foods during pregnancy and lactation is related to health outcomes.
- To examine the potential effects of folate intake at or above the Tolerable Upper Intake Level.
- On folic acid supplementation as an individual nutrient as compared to as a multi-vitamin/mineral or prenatal supplement, and as compared to fortified food, in relation to health outcomes.
- To understand the relationship between folic acid supplementation and during pregnancy and lactation and milk folate levels in folate deficient women and those with adequate levels.
- To understand the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and the risk of gestational diabetes.
- To assess the relationship between folic acid from supplements consumed before and during pregnancy and lactation and
    - child language development, autism spectrum disorder, cognitive development, and social emotional development.
    - child movement/physical development, academic performance, attention-deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression.
- To examine the relationship between folic acid from supplements consumed during lactation and developmental milestones including neurobehavioral development in the child.
- To assess the relationship between folic acid from fortified foods consumed before and during pregnancy and lactation and developmental milestones including neurobehavioral development in the child.

Included articles

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METHODOLOGY

The NESR team used its rigorous, protocol-driven methodology to support the 2020 Dietary Guidelines Advisory Committee in conducting this systematic review.

NESR's systematic review methodology involves:

- Developing a protocol,
- Searching for and selecting studies,
- Extracting data from and assessing the risk of bias of each included study,
- Synthesizing the evidence,
- Developing conclusion statements,
- Grading the evidence underlying the conclusion statements, and
- Recommending future research.

A detailed description of the methodology used in conducting this systematic review is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews, and can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part C: Methodology.[xlvii] This systematic review was peer reviewed by Federal scientists, and information about the peer review process can also be found in the Committee's Report, Part C. Methodology. Additional information about this systematic review, including a description of and rationale for any modifications made to the protocol can be found in the 2020 Dietary Guidelines Advisory Committee Report, Chapter 2. Food, Beverage, and Nutrient Consumption During Pregnancy and Chapter 3. Food, Beverage, and Nutrient Consumption During Lactation.

Below are details of the final protocol for the systematic review described herein, including the:

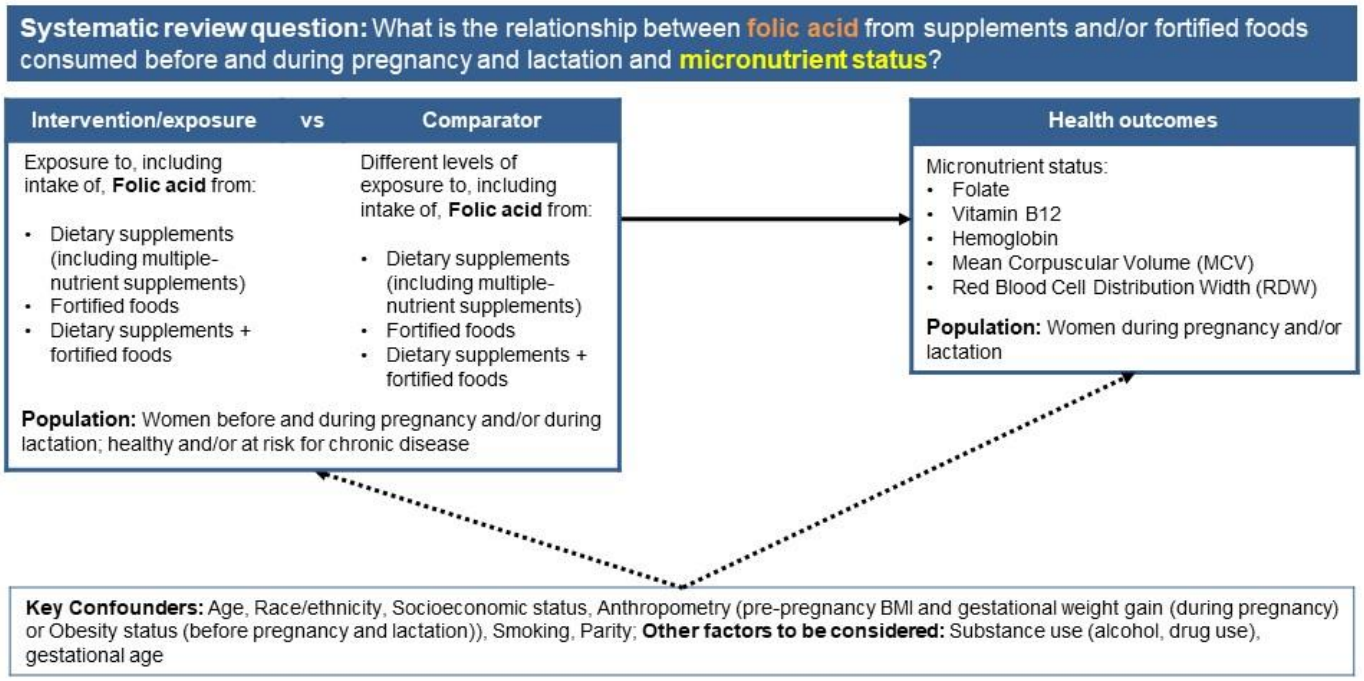
- Analytic framework
- Literature search and screening plan
- Literature search and screening results

ANALYTIC FRAMEWORK

The analytic framework (**Figure 1 through Figure 5**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework were defined and operationalized for the review.

[xlvii] Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

Figure 1. Analytic framework: Folic acid and micronutrient status



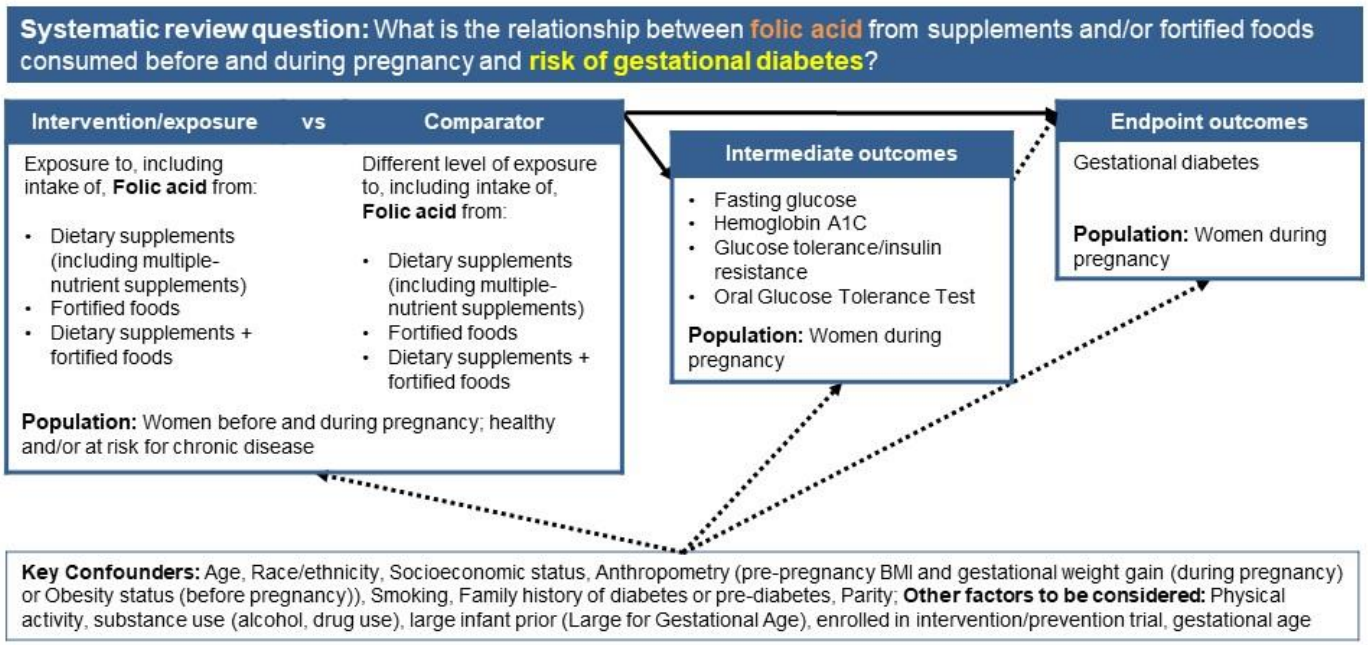
Key definitions

Dietary Supplement - a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS; Dietary Supplement Health and Education Act, 1994)
Fortification - the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. (FDA)
"Before pregnancy" - includes up to 6 months before pregnancy.
Pre-pregnancy BMI - based on health records up to 1 year before and up to and including 1st trimester
Gestational weight gain - weight a woman gains during pregnancy. (CDC)

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

Figure 2. Analytic framework: Folic acid and risk of gestational diabetes



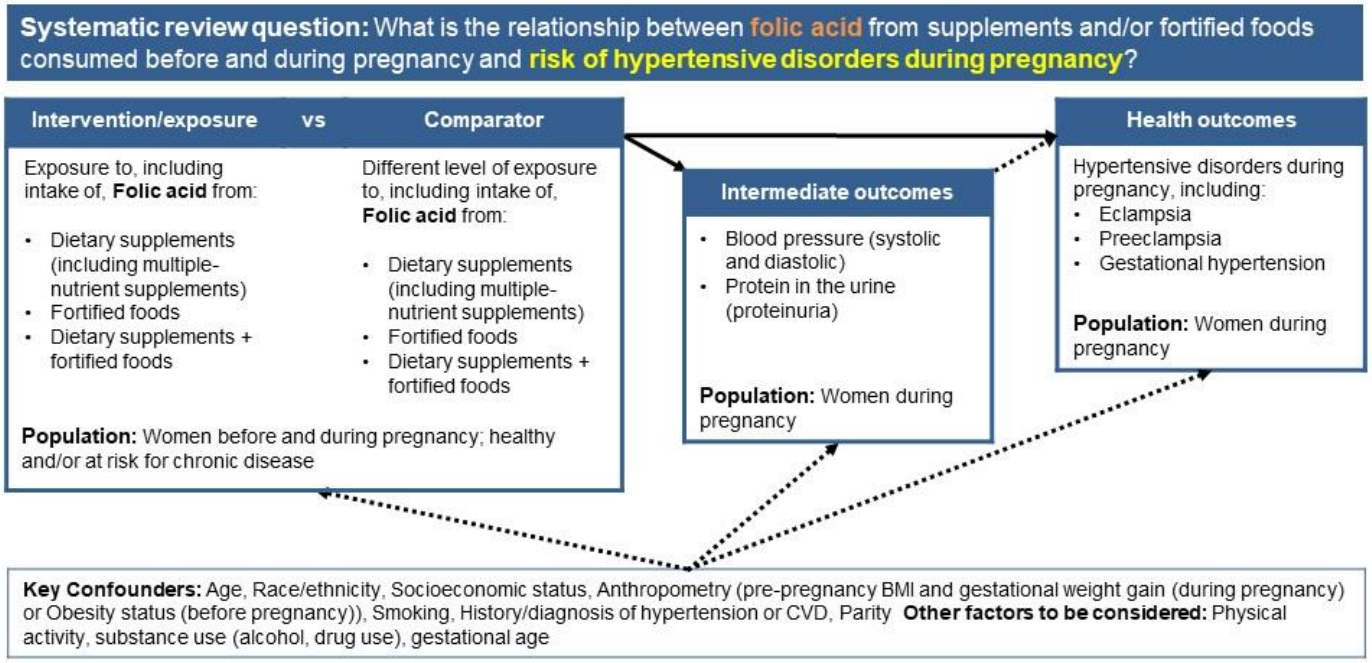
Key definitions

Dietary Supplement - a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS; Dietary Supplement Health and Education Act, 1994)
Fortification - the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. (FDA)
Gestational diabetes - diabetes occurring during pregnancy in women not previously diagnosed with diabetes (Raghavan et al., AJCN, 2019; P/B24 Project)
"Before pregnancy" - includes up to 6 months before pregnancy.
Pre-pregnancy BMI - based on health records up to 1 year before and up to and including 1st trimester
Gestational weight gain - weight a woman gains during pregnancy. (CDC)

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

Figure 3. Analytic framework: Folic acid and risk of hypertensive disorders during pregnancy



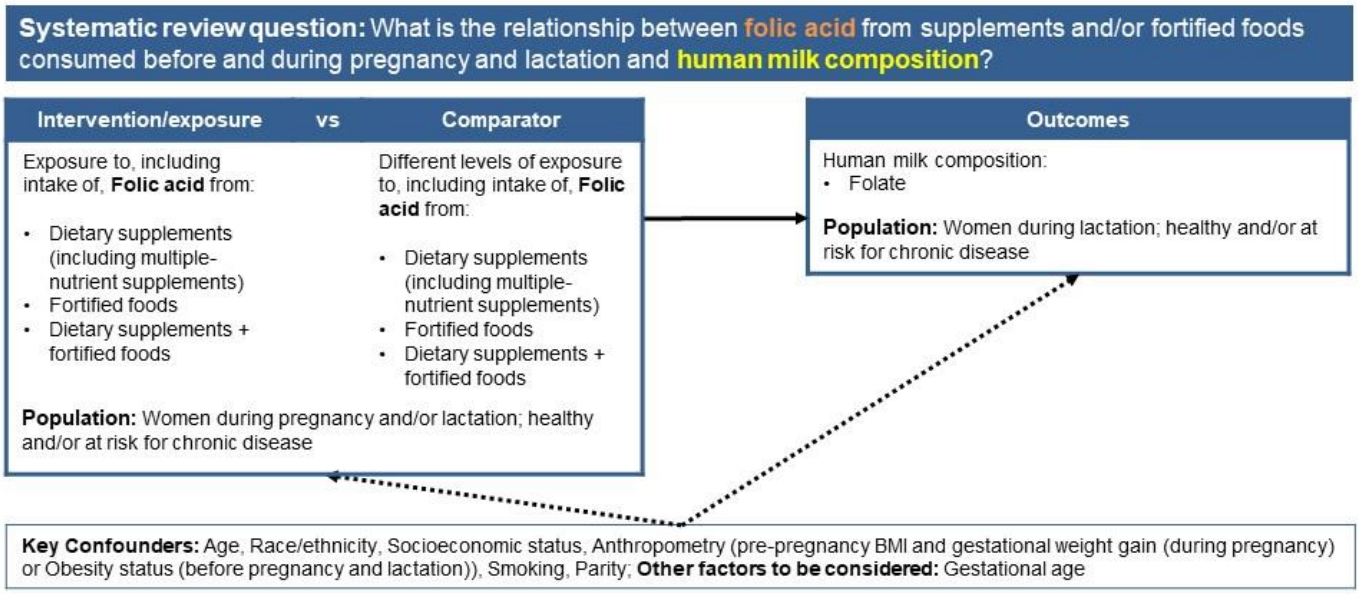
Key definitions

Dietary Supplement - a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS; Dietary Supplement Health and Education Act, 1994)
Fortification - the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. (FDA)
Eclampsia, preeclampsia, gestational hypertension, and **proteinuria** - ACOG 2019 definitions were used.
"Before pregnancy" - includes up to 6 months before pregnancy.
Gestational weight gain - weight a woman gains during pregnancy. (CDC)

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

Figure 4. Analytic framework: Folic acid and human milk composition



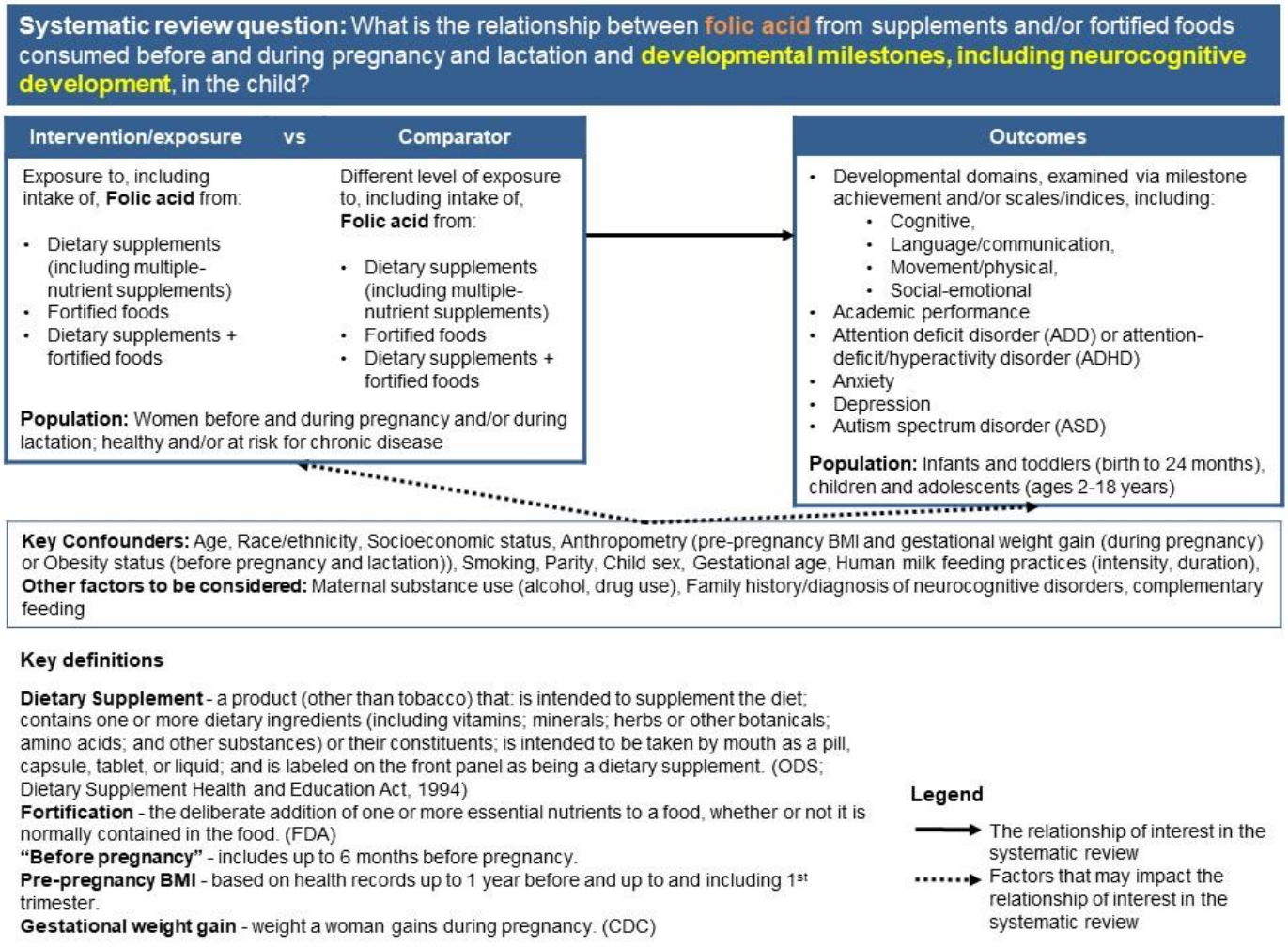
Key definitions

Dietary Supplement - a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS; Dietary Supplement Health and Education Act, 1994)
Fortification - the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. (FDA)
"Before pregnancy" - includes up to 6 months before pregnancy.
Pre-pregnancy BMI - based on health records up to 1 year before and up to and including 1st trimester.
Gestational weight gain - weight a woman gains during pregnancy. (CDC)

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

Figure 5. Analytic framework: Folic acid and developmental milestones, including neurocognitive development, in the child



Key definitions

Dietary Supplement - a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS; Dietary Supplement Health and Education Act, 1994)
Fortification - the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. (FDA)
"Before pregnancy" - includes up to 6 months before pregnancy.
Pre-pregnancy BMI - based on health records up to 1 year before and up to and including 1st trimester.
Gestational weight gain - weight a woman gains during pregnancy. (CDC)

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

LITERATURE SEARCH AND SCREENING PLAN

Inclusion and exclusion criteria

This table provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search were included in or excluded from the systematic review.

Table 24. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Non-randomized controlled trials including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies • Uncontrolled before-and-after studies • Cross-sectional studies (for outcomes: human milk composition)	• Uncontrolled trials • Case-control studies • Cross-sectional studies (for outcomes: micronutrient status, gestational diabetes, hypertensive disorders, developmental milestones, including neurocognitive health) • Narrative reviews • Systematic reviews • Meta-analyses
Intervention/ exposure	• Exposure to, including intake of, folic acid from: o Dietary supplements (including multiple-nutrient supplements) o Fortified foods o Dietary supplements + fortified foods • Folic acid includes all folate species, including 5-MTHF and folinic acid	• Exposure to multiple-micronutrient supplements in which nutrients other than the nutrient of interest vary
Comparator	• Different levels of exposure to, including intake of, folic acid from: o Dietary supplements (including multiple-nutrient supplements) o Fortified foods o Dietary supplements + fortified foods	• No comparator • Exposure to multiple-micronutrient supplements in which nutrients other than the nutrient of interest vary
Outcome: **Micronutrient status**	• Including, but not limited to: o Folate: serum folate, RBC folate, etc. o Vitamin B_{12} o Hemoglobin o Mean Corpuscular Volume (MCV) o Red Blood Cell Distribution Width (RDW), etc.	• N/A

Category	Inclusion Criteria	Exclusion Criteria
Outcome: **Gestational diabetes**	Intermediate outcome: • Fasting glucose • Hemoglobin A1C • Glucose tolerance/insulin resistance • Oral Glucose Tolerance Test Endpoint outcome: • Gestational diabetes	• N/A
Outcome: **Hypertensive disorders**	Intermediate outcome: • Blood pressure (systolic and diastolic) during pregnancy • Protein in the urine (proteinuria) Endpoint outcome: • Eclampsia • Preeclampsia • Gestational hypertension	• N/A
Outcome: **Human milk composition**	• Including, but not limited to: o Folate: total folate, reduced folates, unmetabolized folic acid, etc.	• Human milk from third parties (e.g., banked/donor milk)
Outcome: **Developmental milestones, including neurocognitive development**	• Developmental domains, examined via milestone achievement and/or scales/indices, including: o Cognitive, o Language/communication, o Movement/physical, o Social-emotional • Academic performance • Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD) • Anxiety • Depression • Autism spectrum disorder (ASD)	• N/A
Date of publication (for all outcomes)	• January 1980 – June/July 2019	• Articles published prior to January 1980
Publication status	• Articles that have been peer-reviewed	• Articles that have not been peer-reviewed and are not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, and conference proceedings
Language of publication	• Articles published in English	• Articles published in languages other than English
Country[xlviii]	• Studies conducted in countries ranked as high or very high human development	• Studies conducted in countries ranked as medium or lower human development

[xlviii] The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics

Category	Inclusion Criteria	Exclusion Criteria
Study participants	• Human participants	• Non-human participants (e.g., animal or in-vitro models) • Studies that ***exclusively*** enroll multiple gestation pregnancies or exclusively present combined analyses of singleton and multiple gestations
Life stage of study participants - *intervention or exposure* (relevant for all outcomes)	• Women up to 6 months before pregnancy • Women during pregnancy • Women during lactation	• N/A
Life stage of study participants - *outcomes*: micronutrient status	• Women during pregnancy • Women during lactation	• N/A
Life stage of study participants - *outcomes*: gestational diabetes	• Women during pregnancy	• N/A
Life stage of study participants - *outcomes*: hypertensive disorders	• Women during pregnancy	• N/A
Life stage of study participants - *outcomes*: milk composition	• Women during lactation	• N/A
Life stage of study participants - *outcomes*: developmental milestones including neurocognitive development	• Infants and toddlers (birth – 24 months) • Children and adolescents (2 – 18 years)	• Adults (19 – 64 years) • Older adults (65 years and older)

Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world- country-and-lending-groups).

Category	Inclusion Criteria	Exclusion Criteria

Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity
	• Studies that enroll ***some*** participants diagnosed with a disease or with the health outcome of interest:
	  ○ Gestational diabetes
	  ○ Hypertensive disorders of pregnancy
	  ○ Neurocognitive disorders (ADD, ADHD, anxiety, depression, or ASD)
	  ○ Studies that enroll some participants who are deficient in folate
	• Studies that enroll ***some*** mothers with infants who are born preterm (<37 weeks and 0/7 days gestational age)
	• Studies that ***exclusively*** enroll or enroll ***some*** mothers diagnosed with the outcome of interest that is to be examined in the infant/child (developmental milestones, including neurocognitive development)
		• Studies that ***exclusively*** enroll participants diagnosed with a chronic disease, or hospitalized with an illness or injury. (For this criterion, studies that exclusively enroll participants with obesity will not be excluded.)
		• Studies that ***exclusively*** enroll participants with the outcome of interest (gestational diabetes, hypertensive disorders of pregnancy) (i.e., studies that aim to treat participants who have already been diagnosed with the outcome of interest)
		• Studies that ***exclusively*** enroll infants born preterm (gestational age <37 weeks and 0/7 days), infants with low birth weight (<2500g), and/or infants born small for gestational age

Electronic databases and search terms

Micronutrient status and Human milk composition

PubMed

- Provider: U.S. National Library of Medicine
- Date(s) searched: June 14, 2019
- Date range searched: January 1, 1980 to June 14, 2019
- Search terms:

#1 - "Folic Acid"[Mesh] OR folic acid* OR folate* OR folacin*

#2 - Dietary supplements[mh] OR diet supplement* OR dietary supplement* OR food supplement* OR nutrition supplement* OR nutritional supplement* OR vitamin supplement*[tiab] OR multivitamin*[tiab] OR prenatal vitamin*[tiab] OR maternal vitamin*[tiab]

#3 - "Food, Fortified"[Mesh] OR ((food[mh] OR food[tiab] OR foods[tiab]) AND (fortification[tiab] OR fortified[tiab] OR fortify[tiab] OR fortifies[tiab] OR fortifying[tiab] OR enrich*[tiab])) OR fortified food* OR enriched food* OR enriching food* OR fortifying food* OR food fortification[tiab] OR "folic acid fortified"[tiab] OR folic acid fortified food*

#4 - pregnancy[mh] OR pregnancy complications[mh] OR “Prenatal Exposure Delayed Effects”[mesh] OR “Maternal Exposure”[mesh] OR “pregnant women”[mh] OR pregnan*[tiab] OR pre-pregnancy[tiab] OR prenatal[tiab] OR pre-natal[tiab] OR maternal[tiab] OR mother[tiab] OR mothers[tiab] OR mothers[mh] OR postpartum[tiab] OR perinatal[tiab] OR peri-natal[tiab] OR pre-conception[tiab] OR preconception[tiab] OR peri-conception[tiab] OR periconception[tiab] OR "Peripartum Period"[Mesh] OR peripartum[tiab] OR peri-partum[tiab] OR gestation*[tiab] OR natal[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR puerperium[tiab]

OR "Maternal Nutritional Physiological Phenomena"[Mesh]

#5 - Lactation[mh] OR lactation[tiab] OR lactating[tiab] OR breast feeding[mh] OR breastfeeding[tiab] OR breast feed* OR breast-feed*[tiab] OR breastfed[tiab] OR breast-fed[tiab] OR breastfeed*

#6 - Milk, human[mh] OR "breast milk"[tiab] OR breast-milk[tiab] OR "human milk"[tiab] OR "mother's milk"[tiab] OR "mothers milk"[tiab] OR breastmilk[tiab] OR “human milk composition”[tiab] OR "milk composition"[tiab]

#7 - Micronutrients[mh] OR micronutrient*[tiab] OR vitamin*[tiab] OR vitamins[tiab] OR trace element* OR Iron[mh] OR iron[tiab] OR "Anemia"[Mesh] OR "Anemia"[tiab] OR anemic[tiab] OR iron deficien*[tiab] OR apoferritin*[tiab] OR ferritins[mh] OR ferritin*[tiab] OR ferrous[tiab] OR "Transferrin "[tiab] OR "Vitamin B 12"[Mesh] OR “vitamin B complex”[tiab] OR "Vitamin B 12"[tiab] OR "Vitamin B12"[tiab] OR "Vitamin B 12 Deficiency"[Mesh] OR Cobamide*[tiab] OR Cobalamin*[tiab] OR Cyanocobalamin[tiab] OR eritron[tiab] OR hydroxocobalamin[mh] OR hydroxocobalamin[tiab] OR hemoglobin*[tiab] OR hemoglobins[mh] OR methemoglobin[tiab] OR oxyhemoglobin*[tiab] OR sulfhemoglobin*[tiab] OR mean corpuscular volume[tiab] OR MCV[tiab] OR red blood cell*[tiab] OR rbc[tiab] OR rbcs[tiab] OR RDW[tiab] OR red blood cell distribution width[tiab] OR erythrocyte indices[mh] OR multimicronutrient* OR multi-micronutrient*

#8 - #1 AND (#2 OR #3)

#9 - #4 OR #5

#10 - #6 OR #7

#11 - #8 AND #9 AND #10

#12 - #11 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti])

Filters: Publication date from 1980/01/01 to 2019/06/14, English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) searched: June 14, 2019
- Date range searched: January 1, 1980 to June 14, 2019
- Search terms:

#1 - [mh "folic acid"] OR “folic acid” OR “folic acids” OR folate OR folates OR folacin OR folacins

#2 - [mh “Dietary supplements”] OR “diet supplement” OR “diet supplements” OR “dietary supplement” OR “dietary supplements” OR “food supplement” OR “food supplements” OR “nutrition supplement” OR “nutrition supplements” OR “nutritional supplement” OR “nutritional supplements” OR “vitamin supplement” OR “vitamin supplements” OR multivitamin OR multivitamins OR “prenatal vitamin” OR “prenatal vitamins” OR “maternal vitamins” OR “maternal vitamin” OR “pre-natal vitamin” OR “pre-natal vitamins”

#3 - [mh "Food, Fortified"] OR (([mh food] OR food OR foods) AND (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich*)) OR “fortified food” OR “fortified foods” OR

“enriched food” OR “enriched foods” OR “enriching food” OR “enriching foods” OR “fortifying food” OR “fortifying foods” OR “food fortification” OR "folic acid fortified"

#4 - [mh pregnancy] OR [mh “pregnancy complications”] OR [mh “Prenatal Exposure Delayed Effects”] OR [mh “Maternal Exposure”] OR [mh “pregnant women”] OR pregnan* OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR [mh mothers] OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR [mh "Peripartum Period"] OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR [mh "Maternal Nutritional Physiological Phenomena"]

#5 - [mh Lactation] OR lactation OR lactating OR [mh "breast feeding"] OR breastfeeding OR "breast feed" OR "breast feeds" OR breast-feed OR breast-feeds OR breastfed OR breast-fed OR breastfeed OR breastfeeds

#6 - [mh "milk, human"] OR "breast milk" OR "human milk" OR "mothers milk" OR breastmilk OR "human milk composition" OR "human milk"

#7 - [mh Micronutrients] OR micronutrient* OR vitamin OR vitamins OR “trace element” OR “trace elements” OR [mh Iron] OR iron OR [mh Anemia] OR Anemia OR anemic OR “iron deficiency” OR “iron deficient” OR apoferritin OR apoferritins OR [mh ferritins] OR ferritin OR ferritins OR ferrous OR Transferrin OR [mh “Vitamin B 12”] OR “vitamin B complex” OR “Vitamin B 12” OR “Vitamin B12” OR [mh “Vitamin B 12 Deficiency”] OR Cobamide* OR Cobalamin* OR Cyanocobalamin OR eritron OR [mh hydroxocobalamin] OR hydroxocobalamin OR hemoglobin* OR [mh hemoglobins] OR methemoglobin OR oxyhemoglobin* OR sulfhemoglobin* OR “mean corpuscular volume” OR MCV OR “red blood cell” OR “red blood cells” OR rbc OR rbcs OR RDW OR “red blood cell distribution width” OR [mh “erythrocyte indices”] OR multimicronutrient* OR multi-micronutrient*

#8 - #1 AND (#2 OR #3)

#9 - #4 OR #5

#10 - #6 OR #7

#11 - #8 AND #9 AND #10

Filters: Publication Year from 2000 to 2019, in Trials (Word variations have been searched)

Embase

- Provider: Elsevier
- Date(s) searched: June 18, 2019
- Date range searched: January 1, 1980 to June 18, 2019
- Search terms:

#1 - ('folic acid'/exp OR 'folic acid*':ti,ab OR folate*:ti,ab OR folacin*:ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#2 - ('diet supplementation'/exp OR 'dietary supplement'/exp OR 'diet supplement*':ti,ab OR 'dietary supplement*':ti,ab OR 'food supplement*':ti,ab OR 'nutrition supplement*':ti,ab OR 'nutritional supplement*':ti,ab OR 'vitamin supplement*':ti,ab OR multivitamin*:ti,ab OR 'prenatal vitamin*':ti,ab OR 'maternal vitamin*':ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#3 - ('fortified food'/exp OR (('food'/exp OR foods:ti,ab OR food:ti,ab) AND (fortification:ti,ab OR fortified:ti,ab OR fortify:ti,ab OR fortifies:ti,ab OR fortifying:ti,ab OR enrich*:ti,ab)) OR

'fortified food*':ti,ab OR 'enriched food*':ti,ab OR 'enriching food*':ti,ab OR 'fortifying food*':ti,ab OR 'food fortification':ti,ab OR 'folic acid fortified':ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#4 - (pregnan*:ti,ab OR 'pre pregnancy':ti,ab OR prenatal:ti,ab OR 'pre natal':ti,ab OR maternal:ti,ab OR mother:ti,ab OR mothers:ti,ab OR postpartum:ti,ab OR perinatal:ti,ab OR 'peri natal':ti,ab OR 'pre conception':ti,ab OR preconception:ti,ab OR 'peri conception':ti,ab OR periconception:ti,ab OR peripartum:ti,ab OR 'peri partum':ti,ab OR gestation*:ti,ab OR natal:ti,ab OR antenatal:ti,ab OR 'ante natal':ti,ab OR puerperium:ti,ab OR 'pregnancy'/exp OR 'pregnancy complication'/exp OR 'prenatal exposure'/exp OR 'pregnant woman'/exp OR 'mother'/exp OR 'puerperium'/exp OR 'perinatal period'/exp OR 'maternal nutrition'/exp) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#5 - ('breast feeding'/exp OR 'lactation'/exp OR lactation:ti,ab OR lactating:ti,ab OR breastfeeding:ti,ab OR 'breast feed':ti,ab OR breastfed:ti,ab OR 'breast fed':ti,ab OR breastfeed*:ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#6 - ('breast milk'/exp OR 'breast milk':ti,ab OR 'human milk':ti,ab OR 'mothers milk':ti,ab OR breastmilk:ti,ab OR 'human milk composition':ti,ab OR 'milk composition':ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#7 - ('trace element'/exp OR 'iron'/exp OR 'anemia'/exp OR 'ferritin'/exp OR 'cyanocobalamin'/exp OR 'vitamin b complex'/exp OR 'b12 deficiency'/exp OR 'hemoglobin'/exp OR 'iron deficiency'/exp OR 'apoferritin'/exp OR 'mean corpuscular volume'/exp OR 'red blood cell distribution width'/exp OR 'cobalamin'/exp OR 'cobinamide'/exp OR 'hydroxocobalamin'/exp OR 'oxyhemoglobin'/exp OR micronutrient:ti,ab OR vitamin:ti,ab OR vitamins:ti,ab OR 'trace element':ti,ab OR 'trace elements':ti,ab OR iron:ti,ab OR anemia:ti,ab OR anemic:ti,ab OR 'iron deficiency anemia'/exp OR 'iron deficiency':ti,ab OR apoferritin:ti,ab OR ferritin:ti,ab OR ferritins:ti,ab OR ferrous:ti,ab OR transferrin:ti,ab OR transferrins:ti,ab OR 'vitamin b complex':ti,ab OR 'vitamin b 12':ti,ab OR cobamide:ti,ab OR cobalamin:ti,ab OR cyanocobalamin:ti,ab OR eritron:ti,ab OR hydroxocobalamin:ti,ab OR hemoglobin:ti,ab OR hemoglobins:ti,ab OR methemoglobin:ti,ab OR oxyhemoglobin:ti,ab OR oxyhemoglobins:ti,ab OR sulfhemoglobin:ti,ab OR 'mean corpuscular volume':ti,ab OR mcv:ti,ab OR 'red blood cell':ti,ab OR 'red blood cells':ti,ab OR rbc:ti,ab OR rbcs:ti,ab OR rdw:ti,ab OR 'red blood cell distribution width':ti,ab OR 'erythrocyte indices':ti,ab OR multimicronutrient:ti,ab OR multimicronutrients:ti,ab) AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND [humans]/lim AND [1980-2019]/py

#8 - #1 AND (#2 OR #3)

#9 - #4 OR #5

#10 - #6 OR #7

#11 - #8 AND #9 AND #10

#12 - #11 AND [article]/lim AND [humans]/lim AND [english]/lim AND [1980-2019]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cumulative Index of Nursing and Allied Health Literature (CINAHL Plus)

- Provider: EBSCOhost
- Date(s) searched: June 18, 2019

- Date range searched: January 1, 1980 to June 14, 2019
- Search terms:

#1 - (MH "Folic Acid+" OR "folic acid*" OR folate* OR folacin*)

#2 - (MH "Dietary Supplements+" OR “diet supplement*” OR “dietary supplement*” OR “food supplement*” OR “nutrition supplement*” OR “nutritional supplement*” OR “vitamin supplement*” OR multivitamin* OR “prenatal vitamin*” OR “maternal vitamin*”)

#3 - ((MH "Food, Fortified" OR “fortified food*” OR “enriched food*” OR “enriching food*” OR “fortifying food*” OR “food fortification” OR "folic acid fortified" OR “folic acid fortified food”)) OR ((MH "Food+" OR food OR foods) N6 (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich*)))

#4 - (MH "Pregnancy+" OR MH "Pregnancy Complications+" OR MH "Prenatal Exposure Delayed Effects" OR MH "Maternal Exposure" OR MH "Expectant Mothers" OR pregnan* OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR MH "Mothers" OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR MH "Maternal Nutritional Physiology")

#5 - (MH "Lactation" OR lactation OR lactating OR MH "Breast Feeding" OR breastfeeding OR “breast feed*” OR breast-feed* OR breastfed OR breast-fed OR breastfeed*)

#6 - (MH "Milk, Human" OR "breast milk" OR breast-milk OR "human milk" OR "mother's milk" OR "mothers milk" OR breastmilk OR “human milk composition” OR "milk composition")

#7 - (MH "Micronutrients" OR micronutrient* OR vitamin* OR vitamins OR “trace element*” OR MH "Iron" OR iron OR MH "Anemia" OR anemia OR anemic OR “iron deficien*” OR apoferritin* OR MH "Ferritin" OR ferritin* OR ferrous OR transferrin OR MH "Vitamin B Complex" OR “vitamin B complex” OR "Vitamin B 12" OR "Vitamin B12" OR MH "Vitamin B12 Deficiency" OR Cobamide* OR Cobalamin* OR Cyanocobalamin OR eritron OR hydroxocobalamin OR hemoglobin* OR MH "Hemoglobins" OR methemoglobin OR oxyhemoglobin* OR sulfhemoglobin* OR “mean corpuscular volume” OR mcv OR “red blood cell*” OR rbc OR rbcs OR rdw or “red blood cell distribution width” OR “erythrocyte indices” OR multimicronutrient*

#8 - #1 AND (#2 OR #3)

#9 - #4 OR #5

#10 - #6 OR #7

#11 - #8 AND #9 AND #10

#12 - #11 NOT ((MH "Literature Review" OR MH "Meta Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication))

Filters: English Language, Human, Published Date: 20000101 - 20190614

Gestational diabetes and Hypertensive disorders of pregnancy

PubMed

- Provider: U.S. National Library of Medicine
- Date(s) searched: July 12, 2019
- Date ranged searched: January 1, 1980 to July 12, 2019
- Search terms:

#1 - "Folic Acid"[mh] OR folic acid* OR folate* OR folacin* OR folic acid deficiency[mh]

#2 - "Food, Fortified"[Mesh] OR ((food[mh] OR food[tiab] OR foods[tiab]) AND (fortification[tiab] OR fortified[tiab] OR fortify[tiab] OR fortifies[tiab] OR fortifying[tiab] OR enrich*[tiab] OR supplement*[tiab])) OR fortified food* OR enriched food* OR enriching food* OR fortifying food* OR food fortification[tiab] OR "folic acid fortified"[tiab] OR folic acid fortified food* OR Dietary supplements[mh] OR diet supplement* OR dietary supplement* OR food supplement* OR nutrition supplement* OR nutritional supplement* OR vitamin supplement*[tiab] OR multivitamin*[tiab] OR prenatal vitamin*[tiab] OR maternal vitamin*[tiab] OR vitamins[mh]

#3 - "Pregnancy"[Mesh] OR “Pregnancy Complications”[Mesh] OR “Prenatal Exposure Delayed Effects”[Mesh] OR “Maternal Exposure”[Mesh] OR “pregnant women”[Mesh] OR pregnan*[tiab] OR pre-pregnancy[tiab] OR prenatal[tiab] OR pre-natal[tiab] OR maternal[tiab] OR mother[tiab] OR mothers[tiab] OR “Mothers”[Mesh] OR postpartum[tiab] OR perinatal[tiab] OR peri-natal[tiab] OR pre-conception[tiab] OR preconception[tiab] OR peri-conception[tiab] OR periconception[tiab] OR "Peripartum Period"[Mesh] OR peripartum[tiab] OR peri-partum[tiab] OR gestation*[tiab] OR natal[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR puerperium[tiab] OR "Maternal Nutritional Physiological Phenomena"[Mesh] OR "Postpartum Period"[Mesh] OR postpartum[tiab] OR post-partum[tiab] OR perinatal OR peri-natal OR puerperium[tiab] OR postpartal OR post-partal OR postnatal OR post delivery[tiab] OR after birth[tiab]

#4 - “Diabetes, Gestational"[Mesh] OR (gestation*[tiab] AND (diabete*[tiab] OR diabetic*[tiab] OR pre-diabet*[tiab] OR prediabet*[tiab] OR blood sugar*[tiab] OR blood glucose[mh])) OR “fasting glucose”[tiab] OR “impaired fasting”[tiab] OR “fasting blood glucose”[tiab] OR “hemoglobin A1C”[tiab] OR “ haemoglobin A1c” OR hba1c[tiab] OR “hba 1c”[tiab]OR glycated hemoglobin A[mh] OR glucose toleran* OR glucose intoleran*[tiab] OR glucose intolerance[mh] OR insulin resistance[mh] OR insulin resistan*[tiab] OR dysglycemi*[tiab] OR prediabetic state[mh] OR prediabet*[tiab] OR hyperglycemia[mh] OR hyperglycemi*[tiab] OR hyperinsulinism[mh] OR hyperinsulin*[tiab] OR diabet*[tiab] OR diabetes mellitus[mh:noexp] OR blood sugar*[tiab] OR hypertensi*[tiab] OR "Hypertension"[Mesh:NoExp] OR hypertension, pregnancy induced[mh] OR pregnancy induced hypertens*[tiab] OR "Proteinuria"[Mesh:noexp] OR proteinuri*[tiab] OR albuminuria[mh] OR Albuminuria[tiab] OR "Blood Pressure"[mh] OR “blood pressure”[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR eclampsia*[tiab] OR pre-eclampsia[tiab] OR preeclampsia[tiab] OR pre-eclamptic[tiab] OR preeclamptic[tiab] OR eclamptic[tiab]

#5 - #1 AND #2

#6 - #5 AND #3

#7 - #6 AND #4

#8 - #7 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti])

Filters: Publication date from 1980/01/01 to 2019/07/12; English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) searched: July 12, 2019
- Date ranged searched: January 1, 1980 to July 12, 2019
- Search terms:

#1 - [mh “Folic Acid"] OR “folic acid” OR “folic acids” OR folate OR folates OR folacin OR folacins OR [mh “folic acid deficiency”]

#2 - [mh "Food, Fortified"] OR (([mh food] OR food OR foods) AND (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich* OR supplement*)) OR “fortified food” OR “fortified foods” OR “enriched food” OR “enriched foods” OR “enriching food” OR “enriching foods” OR “fortifying food” OR “fortifying foods” OR “food fortification” OR "folic acid fortified"

#3 - [mh “Dietary supplements”] OR diet supplement* OR dietary supplement* OR food supplement* OR nutrition supplement* OR nutritional supplement* OR vitamin supplement*[tiab] OR multivitamin*[tiab] OR prenatal vitamin*[tiab] OR maternal vitamin*[tiab]

#4 - [mh "Pregnancy"] OR [mh "Pregnancy Complications"] OR [mh "Prenatal Exposure Delayed Effects"] OR [mh "Maternal Exposure"] OR [mh "Pregnant Women"] OR [mh "Mothers"] OR [mh "Peripartum Period"] OR [mh "Maternal Nutritional Physiological Phenomena"] OR [mh "Postpartum Period"] OR (pregnancy OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR postpartum OR post-partum OR perinatal OR peri-natal OR puerperium OR postpartal OR post-partal OR postnatal OR “post delivery” OR “after birth”):ti,ab,kw

#5 - [mh "Diabetes, Gestational"] OR (gestation*NEAR/4 (diabete* OR diabetic* OR pre-diabet*OR prediabet* OR “blood sugar” OR “blood glucose” OR [mh “blood glucose”])) OR “fasting glucose” OR “impaired fasting” OR “fasting blood glucose” OR “hemoglobin A1C” OR “ haemoglobin A1c” OR hba1c OR “hba 1c” OR [mh “glycated hemoglobin A”] OR “glucose toleran*” OR “glucose intoleran*” OR [mh “glucose intolerance”] OR [mh “insulin resistance] OR “insulin resistan*” OR dysglycemi* OR [mh “prediabetic state”] OR prediabet* OR [mh “hyperglycemia”] OR hyperglycemi* OR [mh “hyperinsulinism”] OR hyperinsulin* OR diabet* OR “blood sugar*” OR Hypertension OR hypertensive OR [mh "Hypertension"] OR [mh “hypertension, pregnancy induced”] OR “pregnancy induced hypertension” OR [mh"Proteinuria"] OR proteinuri* OR [mh “albuminuria”] OR Albuminuria OR [mh "Blood Pressure"] OR “blood pressure” OR “systolic pressure” OR “diastolic pressure” OR eclampsia* OR pre-eclampsia OR preeclampsia OR pre-eclamptic OR preeclamptic OR eclamptic OR [mh “eclampsia”]

#6 - #1 AND (#2 OR #3)

#7 - #6 AND #4

#8 - #7 AND #5

Filters: publication year from 2000 to 2019, Trials

Embase

- Provider: Elsevier
- Date(s) searched: July 12, 2019

- Date ranged searched: January 1, 1980 to July 12, 2019
- Search terms:

#1 - ('folic acid'/exp OR 'folic acid*':ti,ab OR folate*:ti,ab OR folacin*:ti,ab OR 'folic acid deficiency'/de) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#2 - ('diet supplementation'/exp OR 'dietary supplement'/exp OR 'diet supplement*':ti,ab OR 'dietary supplement*':ti,ab OR 'food supplement*':ti,ab OR 'nutrition supplement*':ti,ab OR 'nutritional supplement*':ti,ab OR 'vitamin supplement*':ti,ab OR multivitamin*:ti,ab OR 'prenatal vitamin*':ti,ab OR 'maternal vitamin*':ti,ab OR 'fortified food'/exp OR (('food'/exp OR foods:ti,ab OR food:ti,ab) AND (fortification:ti,ab OR fortified:ti,ab OR fortify:ti,ab OR fortifies:ti,ab OR fortifying:ti,ab OR enrich*:ti,ab)) OR 'fortified food*':ti,ab OR 'enriched food*':ti,ab OR 'enriching food*':ti,ab OR 'fortifying food*':ti,ab OR 'food fortification':ti,ab OR 'folic acid fortified':ti,ab) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#3 - (pregnancy:ab,ti OR 'pre pregnancy':ab,ti OR prenatal:ab,ti OR 'pre natal':ab,ti OR maternal:ab,ti OR mother:ab,ti OR mothers:ab,ti OR 'pre conception':ab,ti OR preconception:ab,ti OR 'peri conception':ab,ti OR periconception:ab,ti OR peripartum:ab,ti OR 'peri partum':ab,ti OR gestation*:ab,ti OR natal:ab,ti OR antenatal:ab,ti OR 'ante natal':ab,ti OR postpartum:ab,ti OR post-partum:ab,ti OR perinatal:ab,ti OR 'peri natal':ab,ti OR puerperium:ab,ti OR postpartal:ab,ti OR post-partal:ab,ti OR postnatal:ab,ti OR 'post delivery':ab,ti OR 'after birth':ab,ti OR 'pregnancy'/exp/mj OR 'pregnancy complication'/exp/mj OR 'prenatal exposure'/mj OR 'maternal exposure'/mj OR 'pregnant woman'/mj OR 'mother'/mj OR 'puerperium'/exp/mj OR 'maternal nutrition'/mj) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#4 - ((('maternal diabetes mellitus':ti,ab OR (gestation*:ti,ab AND ((diabete*:ti,ab OR diabetic*:ti,ab OR 'pre diabet*':ti,ab OR prediabet*:ti,ab OR blood) AND sugar*:ti,ab OR 'glucose blood level'/exp)) OR 'fasting glucose':ti,ab OR 'impaired fasting':ti,ab OR 'fasting blood glucose':ti,ab OR 'hemoglobin a1c':ti,ab OR haemoglobin) AND a1c:ti,ab OR hb) AND alc:ti,ab OR hba1c:ti,ab OR 'glucose toleran*':ti,ab OR 'glucose intoleran*':ti,ab OR 'insulin resistan*':ti,ab OR dysglycemi*:ti,ab OR prediabet*:ti,ab OR hyperglycemi*:ti,ab OR hyperglycaemi*:ti,ab OR hyperinsulin*:ti,ab OR diabet*:ti,ab OR 'blood sugar*':ti,ab OR 'diabetes mellitus gravidarum':ti,ab OR 'pregnancy diabetes mellitus'/exp OR 'hemoglobin a1c'/exp OR 'glucose intolerance'/exp OR 'insulin resistance'/exp OR 'impaired glucose tolerance'/exp OR 'hyperglycemia'/exp OR 'hyperinsulinism'/de OR 'hyperinsulinemia'/de OR 'diabetes mellitus'/de OR hypertensi*:ti,ab OR 'pregnancy induced hypertens*':ti,ab OR proteinuri*:ti,ab OR albuminuria:ti,ab OR 'blood pressure':ti,ab OR 'systolic pressure*':ti,ab OR 'diastolic pressure*':ti,ab OR eclampsia*:ti,ab OR 'pre eclampsia':ti,ab OR preeclampsia:ti,ab OR 'pre eclamptic':ti,ab OR preeclamptic:ti,ab OR eclamptic:ti,ab OR 'hypertension'/de OR 'prehypertension'/de OR 'maternal hypertension'/exp OR 'elevated blood pressure'/de OR 'proteinuria'/exp OR 'eclampsia and preeclampsia'/exp OR 'pregnancy toxemia'/de OR 'pregnancy toxemia*':ti,ab OR 'pregnancy toxaemia*':ti,ab OR 'toxicosis gravidarum':ti,ab OR (((pregnancy OR eclampt* OR eclamps* OR gestation* OR gravidarum) NEAR/4 (toxem* OR toxaem*)):ti,ab)) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py

#5 - #1 AND #2

#6 - #5 AND #3

#7 - #6 AND #4

#8 - #7 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2019]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cumulative Index of Nursing and Allied Health Literature (CINAHL Plus)

- Provider: EBSCOhost
- Date(s) searched: July 12, 2019
- Date ranged searched: January 1, 1980 to July 12, 2019
- Search terms:

#1 - (MH "folic acid") OR “folic acid” OR “folic acids” OR folate OR folates OR folacin OR folacins OR (MH "Folic Acid Deficiency")

#2 - ((MH "Food, Fortified" OR “fortified food*” OR “enriched food*” OR “enriching food*” OR “fortifying food*” OR “food fortification” OR "folic acid fortified" OR “folic acid fortified food”)) OR ((MH "Food+" OR food OR foods) N6 (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich* OR supplement*))

#3 - (MH "Dietary Supplements+" OR “diet supplement*” OR “dietary supplement*” OR “food supplement*” OR “nutrition supplement*” OR “nutritional supplement*” OR “vitamin supplement*” OR multivitamin* OR “prenatal vitamin*” OR “maternal vitamin*” OR (MH “vitamins”)

#4 - pregnancy OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR postpartum OR post-partum OR perinatal OR peri-natal OR puerperium OR postpartal OR post-partal OR postnatal OR “post delivery” OR “after birth” OR (MH "Pregnancy+") OR (MH "Pregnancy Complications") OR (MH "Prenatal Exposure Delayed Effects") OR (MH "Maternal Exposure") OR (MH "Expectant Mothers") OR (MH "Mothers") OR (MH "Puerperium") OR (MH "Maternal Nutritional Physiology") OR (MH "Postnatal Period")

#5 - (MH "Diabetes Mellitus, Gestational")OR (MH "Hemoglobin A, Glycosylated") OR (MH "Glucose Intolerance") OR (MH "Insulin Resistance") OR (MH "Prediabetic State") OR (MH "Hyperglycemia") OR "hyperglycemia" OR (MH "Hyperinsulinism") OR (MH "Hyperinsulinemia") OR (MH "Hypertension") OR (MH "Proteinuria") OR (MH "Albuminuria") OR (MH "Blood Pressure") OR (MH "Eclampsia") OR (MH "Pre-Eclampsia") OR (MH "HELLP Syndrome")OR (gestation* N5 (diabete* OR diabetic* OR pre-diabet* OR prediabet* OR “blood sugar” OR (MH "Blood Glucose"))) OR “fasting glucose” OR “impaired fasting” OR “fasting blood glucose” OR “hemoglobin A1C” OR “haemoglobin A1c” OR hbalc OR hba1c OR “glucose intoleran*” OR “glucose toleran*” OR “insulin resistance” OR dysglycemic OR dysglycemia OR “prediabetic state” OR prediabet* OR hyperglycemia OR hyperinsulin* OR diabet* OR “blood sugar” OR “blood sugars” OR hypertensi* OR “pregnancy induced hypertension” OR proteinuria OR Albuminuria OR “blood pressure” OR “systolic pressure*” OR “diastolic pressure*” OR eclampsia* OR pre-eclampsia OR preeclampsia OR pre-eclamptic OR preeclamptic OR eclamptic

#6 - #1 AND (#2 OR #3)

#7 - #6 AND #4

#8 - #7 AND #5

#9 - #8 NOT (MH "Literature Review" OR MH "Meta Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication")
Filters: English Language, Human, Published Date: 20000101 - 20190712

Developmental milestones, including neurocognitive development

PubMed

- Provider: U.S. National Library of Medicine
- Date(s) searched: July 3, 2019
- Date ranged searched: January 1, 1980 to July 3, 2019
- Search terms:

#1 - "Folic Acid"[mh] OR folic acid* OR folate* OR folacin* OR folic acid deficiency[mh]

#2 - "Food, Fortified"[Mesh] OR ((food[mh] OR food[tiab] OR foods[tiab]) AND (fortification[tiab] OR fortified[tiab] OR fortify[tiab] OR fortifies[tiab] OR fortifying[tiab] OR enrich*[tiab] OR supplement*[tiab])) OR fortified food* OR enriched food* OR enriching food* OR fortifying food* OR food fortification[tiab] OR "folic acid fortified"[tiab] OR folic acid fortified food* OR Dietary supplements[mh] OR diet supplement* OR dietary supplement* OR food supplement* OR nutrition supplement* OR nutritional supplement* OR vitamin supplement*[tiab] OR multivitamin*[tiab] OR prenatal vitamin*[tiab] OR maternal vitamin*[tiab] OR vitamins[mh]

#3 - ("Pregnancy"[Mesh] OR “Pregnancy Complications”[Mesh] OR “Prenatal Exposure Delayed Effects”[Mesh] OR “Maternal Exposure”[Mesh] OR “pregnant women”[Mesh] OR pregnan*[tiab] OR pre-pregnancy[tiab] OR prenatal[tiab] OR pre-natal[tiab] OR maternal[tiab] OR mother[tiab] OR mothers[tiab] OR “Mothers”[Mesh] OR postpartum[tiab] OR perinatal[tiab] OR peri-natal[tiab] OR pre-conception[tiab] OR preconception[tiab] OR peri-conception[tiab] OR periconception[tiab] OR "Peripartum Period"[Mesh] OR peripartum[tiab] OR peri-partum[tiab] OR gestation*[tiab] OR natal[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR puerperium[tiab] OR "Maternal Nutritional Physiological Phenomena"[Mesh] OR "Postpartum Period"[Mesh] OR postpartum[tiab] OR post-partum[tiab] OR perinatal OR peri-natal OR puerperium[tiab] OR postpartal OR post-partal OR postnatal OR post delivery[tiab] OR after birth[tiab] OR "Lactation"[Mesh] OR lactation[tiab] OR lactating[tiab] OR "Breast Feeding"[Mesh] OR breastfeeding[tiab] OR breast-feeding[tiab] OR breast feed* OR breast-feed*[tiab] OR breastfed[tiab] OR breast-fed[tiab] OR breastfeed* OR "Milk, Human"[Mesh] OR human milk[tiab] OR nursing women[tiab]))

#4 - "Mental Disorders"[Mesh] OR mental disorder*[tiab] OR "Cognition"[Mesh] OR cognition[tiab] OR cognitive[tiab] OR metacognition[tiab] OR neurocognitive[tiab] OR neurodevelop*[tiab] OR neurological[tiab] OR "Cognitive Dysfunction"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR depression[tiab] OR "Psychomotor Performance"[Mesh] OR motor skill*[tiab] OR "Executive Function"[Mesh] OR executive function* OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh] OR attention deficit disorder*[tiab] OR ADHD[tiab] OR "Child Behavior Disorders"[Mesh] OR developmental disorder*[tiab] OR "Autism Spectrum Disorder"[Mesh] OR Autism[tiab] OR Asperger[tiab] OR language processing[tiab] OR language delay* OR "Child Development"[Mesh] OR child

develop*[tiab] OR "Developmental Disabilities"[Mesh] OR developmental delay[tiab] OR developmental disabilit*[tiab] OR "Motor Skills Disorders"[Mesh] OR motor skill*[tiab] OR "Problem Solving"[Mesh] OR developmental domain* OR academic performance[tiab] OR academic achievement[tiab] OR academic failure[tiab] OR academic success*[tiab] OR Growth[mh:noexp] OR "Growth Charts"[Mesh] OR "growth and development" [Subheading] OR "growth and development"[tiab] OR "Growth and Development"[Mesh:noexp] OR "Growth"[tiab] OR development*[tiab] OR "Child Development"[Mesh] OR movement[mh] OR "Motor Skills"[Mesh] OR "Nonverbal Communication"[Mesh] OR Standing[tiab] OR sitting[tiab] OR walking[tiab] OR crawling[tiab] OR Ages and Stages Questionnaire* OR ASQ[tiab] OR developmental delay[mh] OR “bayley scales”[tiab] OR verbal behavior[mh] OR talk*[tiab]

#5 - #1 AND #2

#6 - #5 AND #3

#7 - #6 AND #4

#8 - #7 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti]) Filters: Publication date from 1980/01/01 to 2019/07/03; English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) searched: July 3, 2019
- Date ranged searched: January 1, 1980 to July 3, 2019
- Search terms:

#1 - [mh “Folic Acid"] OR “folic acid” OR “folic acids” OR folate OR folates OR folacin OR folacins OR [mh “folic acid deficiency”]

#2 - [mh "Food, Fortified"] OR (([mh food] OR food OR foods) AND (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich* OR supplement*)) OR “fortified food” OR “fortified foods” OR “enriched food” OR “enriched foods” OR “enriching food” OR “enriching foods” OR “fortifying food” OR “fortifying foods” OR “food fortification” OR "folic acid fortified" OR [mh “Dietary supplements”] OR diet supplement* OR dietary supplement* OR food supplement* OR nutrition supplement* OR nutritional supplement* OR vitamin supplement*[tiab] OR multivitamin*[tiab] OR prenatal vitamin*[tiab] OR maternal vitamin*[tiab]

#3 - [mh "Pregnancy"] OR [mh "Pregnancy Complications"] OR [mh "Prenatal Exposure Delayed Effects"] OR [mh "Maternal Exposure"] OR [mh "Pregnant Women"] OR [mh "Mothers"] OR [mh "Peripartum Period"] OR [mh "Maternal Nutritional Physiological Phenomena"] OR [mh "Postpartum Period"] OR [mh Lactation] OR [mh "Breast Feeding"] OR [mh "Milk, Human"] OR (pregnancy OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR postpartum OR post-partum OR perinatal OR peri-natal OR puerperium OR postpartal OR post-partal OR postnatal OR “post delivery” OR “after birth” OR lactation OR lactating OR breastfeeding OR breast-feeding OR breast feed* OR breast-feed* OR breastfed OR breast-fed OR breastfeed OR

“human milk” OR “nursing women”):ti,ab,kw

#4 - [mh ^Growth] OR [mh "Child Development"] OR [mh "Growth Charts"] OR "growth and development" OR [mh ^"Growth and Development"] OR [mh "Child Development"] OR (child NEAR/1 develop*):ti,ab OR [mh movement] OR [mh "Motor Skills"] OR [mh "Nonverbal Communication"] OR "Bayley Scales of Infant Development" OR Standing OR stands OR sits OR sitting OR walk OR walking OR crawling OR crawl OR “Ages and Stages Questionnaire” OR ASQ OR [mh "Mental Disorders"] OR [mh Cognition] OR [mh "Cognitive Dysfunction"] OR [mh "Depressive Disorder"] OR [mh Depression] OR [mh "Psychomotor Performance"] OR [mh "Executive Function"] OR [mh "Attention Deficit and Disruptive Behavior Disorders"] OR [mh "Child Behavior Disorders"] OR [mh "Autism Spectrum Disorder"] OR [mh "Child Development"] OR [mh "Developmental Disabilities"] OR [mh "Motor Skills Disorders"] OR [mh "Problem Solving"] OR (“mental disorder*” OR cognition OR cognitive OR metacognition OR neurocognitive OR neurodevelop* OR neurological OR depression OR anxiety OR motor skill* OR “attention deficit disorder*” OR ADHD OR “developmental disorder*” OR Autism OR Asperger OR “language processing” OR “language delay*” OR “child develop*” OR “developmental delay” OR “developmental disabilit*” OR “motor skill*” OR “developmental domain*” OR “academic performance” OR “academic achievement” OR “academic failure” OR “academic success*”):ti,ab,kw

#5 - #1 AND #2

#6 - #5 AND #3

#7 - #6 AND #4

Filters: publication year from 2000 to 2019, Trials

Embase

- Provider: Elsevier
- Date(s) searched: July 3, 2019
- Date ranged searched: January 1, 1980 to July 3, 2019
- Search terms:

#1 - ('folic acid'/exp OR 'folic acid*':ti,ab OR folate*:ti,ab OR folacin*:ti,ab OR 'folic acid deficiency'/de)

#2 - ('diet supplementation'/exp OR 'dietary supplement'/exp OR 'diet supplement*':ti,ab OR 'dietary supplement*':ti,ab OR 'food supplement*':ti,ab OR 'nutrition supplement*':ti,ab OR 'nutritional supplement*':ti,ab OR 'vitamin supplement*':ti,ab OR multivitamin*:ti,ab OR 'prenatal vitamin*':ti,ab OR 'maternal vitamin*':ti,ab) OR ('fortified food'/exp OR (('food'/exp OR foods:ti,ab OR food:ti,ab) AND (fortification:ti,ab OR fortified:ti,ab OR fortify:ti,ab OR fortifies:ti,ab OR fortifying:ti,ab OR enrich*:ti,ab)) OR 'fortified food*':ti,ab OR 'enriched food*':ti,ab OR 'enriching food*':ti,ab OR 'fortifying food*':ti,ab OR 'food fortification':ti,ab OR 'folic acid fortified':ti,ab)

#3 - pregnancy:ab,ti OR 'pre pregnancy':ab,ti OR prenatal:ab,ti OR 'pre natal':ab,ti OR maternal:ab,ti OR mother:ab,ti OR mothers:ab,ti OR 'pre conception':ab,ti OR preconception:ab,ti OR 'peri conception':ab,ti OR periconception:ab,ti OR peripartum:ab,ti OR 'peri partum':ab,ti OR gestation*:ab,ti OR natal:ab,ti OR antenatal:ab,ti OR 'ante natal':ab,ti OR postpartum:ab,ti OR post-partum:ab,ti OR perinatal:ab,ti OR 'peri natal':ab,ti OR puerperium:ab,ti OR postpartal:ab,ti OR post-partal:ab,ti OR postnatal:ab,ti OR 'post delivery':ab,ti OR 'after birth':ab,ti OR lactation:ab,ti OR lactating:ab,ti OR breastfeeding:ab,ti

OR breast-feeding:ab,ti OR 'breast feed*':ab,ti OR breastfed:ab,ti OR 'breast fed':ab,ti OR breastfeed:ab,ti OR 'human milk':ab,ti OR 'nursing women':ab,ti OR 'pregnancy'/exp/mj OR 'pregnancy complication'/exp/mj OR 'prenatal exposure'/mj OR 'maternal exposure'/mj OR 'pregnant woman'/mj OR 'mother'/mj OR 'puerperium'/exp/mj OR 'maternal nutrition'/mj OR 'lactation'/mj OR 'breast feeding'/exp/mj OR 'breast milk'/exp/mj

#4 - 'mental disorder*':ab,ti OR cognition:ab,ti OR cognitive:ab,ti OR metacognition:ab,ti OR neurocognitive:ab,ti OR neurodevelop*:ab,ti OR neurological:ab,ti OR depression:ab,ti OR 'motor skill*':ab,ti OR 'executive function':ab,ti OR 'attention deficit disorder':ab,ti OR adhd:ab,ti OR 'developmental disorder':ab,ti OR 'language processing':ab,ti OR 'language delay*':ab,ti OR 'child develop*':ab,ti OR autism:ab,ti OR asperger:ab,ti OR 'developmental delay':ab,ti OR 'developmental disabilit*or developmental domain*':ab,ti OR 'academic performance':ab,ti OR 'academic achievement':ab,ti OR 'academic failure':ab,ti OR 'academic success*':ab,ti OR 'mental disease'/exp OR 'cognition'/exp OR 'cognitive defect'/exp OR 'depression'/exp OR 'anxiety'/exp OR 'psychomotor performance'/exp OR 'executive function'/exp OR 'attention deficit disorder'/exp OR 'behavior disorder'/exp OR 'autism'/exp OR 'child development'/exp OR 'developmental disorder'/exp OR 'psychomotor disorder'/exp OR 'problem solving'/exp OR growth and development:ti,ab OR growth:ti,ab OR develop*:ti,ab OR ‘child develop*’:ti,ab OR standing:ti,ab OR sitting:ti,ab OR walking:ti,ab OR crawling:ti,ab OR crawl:ti,ab OR asq:ti,ab OR ‘ages and stages questionnaire’:ti,ab OR child develop*:ti,ab OR motor develop*:ti,ab OR ‘motor skill*’:ti,ab OR ‘motor function’:ti,ab OR ‘motor ability’:ti,ab OR ‘motor performance’:ti,ab OR ‘postnatal development’:ti,ab OR ‘Ages and Stages Questionnaire’*:ti,ab OR ASQ:ti,ab OR ‘bayley scale*’:ti,ab OR talk*:ti,ab]OR 'postnatal growth'/exp OR ‘human development’/exp OR 'postnatal development'/exp OR 'motor performance'/exp OR 'nonverbal communication'/exp OR 'verbal behavior'/exp OR 'standing'/exp OR 'sitting'/exp OR 'walking'/exp OR 'crawling'/exp OR 'growth chart'/exp

#5 - #1 AND #2

#6 - #5 AND #3

#7 - #6 AND #4

#8 - #7 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [2000-2019]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cumulative Index of Nursing and Allied Health Literature (CINAHL Plus)

- Provider: EBSCOhost
- Date(s) searched: July 3, 2019
- Date ranged searched: January 1, 1980 to July 3, 2019
- Search terms:

#1 - (MH "folic acid") OR “folic acid” OR “folic acids” OR folate OR folates OR folacin OR folacins OR (MH "Folic Acid Deficiency")

#2 - ((MH "Food, Fortified" OR “fortified food*” OR “enriched food*” OR “enriching food*” OR “fortifying food*” OR “food fortification” OR "folic acid fortified" OR “folic acid fortified food”)) OR ((MH "Food+" OR food OR foods) N6 (fortification OR fortified OR fortify OR fortifies OR fortifying OR enrich* OR supplement*)) OR (MH "Dietary Supplements+" OR “diet supplement*” OR “dietary supplement*” OR “food supplement*” OR “nutrition supplement*”

OR “nutritional supplement*” OR “vitamin supplement*” OR multivitamin* OR “prenatal vitamin*” OR “maternal vitamin*” OR (MH “vitamins”)

#3 - pregnancy OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother OR mothers OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestation* OR natal OR antenatal OR ante-natal OR puerperium OR postpartum OR post-partum OR perinatal OR peri-natal OR puerperium OR postpartal OR post-partal OR postnatal OR “post delivery” OR “after birth” OR lactation OR lactating OR breastfeeding OR breast-feeding OR breast feed* OR breast-feed* OR breastfed OR breast-fed OR breastfeed OR “human milk” OR “nursing women” OR (MH "Pregnancy+") OR (MH "Pregnancy Complications") OR (MH "Prenatal Exposure Delayed Effects") OR (MH "Maternal Exposure") OR (MH "Expectant Mothers") OR (MH "Mothers") OR (MH "Puerperium") OR (MH "Maternal Nutritional Physiology") OR (MH "Postnatal Period") OR (MH "Lactation") OR (MH "Breast Feeding") OR (MH "Milk, Human")

#4 - (MH "Mental Disorders") OR mental disorder* OR (MH "Cognition") OR cognition OR cognitive OR metacognition OR neurocognitive OR neurodevelop* OR neurological OR “cognitive dysfunction” OR “depressive disorders OR (MH "Depression") OR depression OR (MH "Anxiety") OR anxiety OR (MH "Psychomotor Performance") OR motor skill* OR (MH "Executive Function") OR executive function* OR (MH "Attention Deficit Hyperactivity Disorder") OR attention deficit disorder* OR ADHD OR (MH "Child Behavior Disorders") OR developmental disorder* OR (MH "Autistic Disorder") OR autism OR Asperger OR “language processing” OR language delay* OR (MH "Child Development") OR child develop* OR (MH "Developmental Disabilities") OR developmental delay* OR developmental disabilit* OR (MH "Motor Skills Disorders") OR motor skill* OR (MH "Problem Solving") OR developmental domain* OR “academic performance” OR “academic achievement” OR “academic failure” OR academic success* OR “growth and development” OR growth OR develop* OR “child develop*” OR movement OR “motor skills” OR ”motor development” OR ”motor skill*” OR ”motor function” OR ”motor ability” OR ”motor performance” OR “growth chart*” OR “infant development” OR “language development” OR standing OR stands OR sitting OR sits OR walking OR walk OR crawling OR crawl OR “ages and stages questionnaire*” OR ASQ OR “bayley scales of infant development” OR (MH "Growth+") OR (MH "Human Development+") OR (MH "Language Development") OR (MH "Nonverbal Communication+") OR (MH "Psychomotor Performance+") OR (MH "Locomotion+")

#5 - #1 AND #2

#6 - #5 AND #3

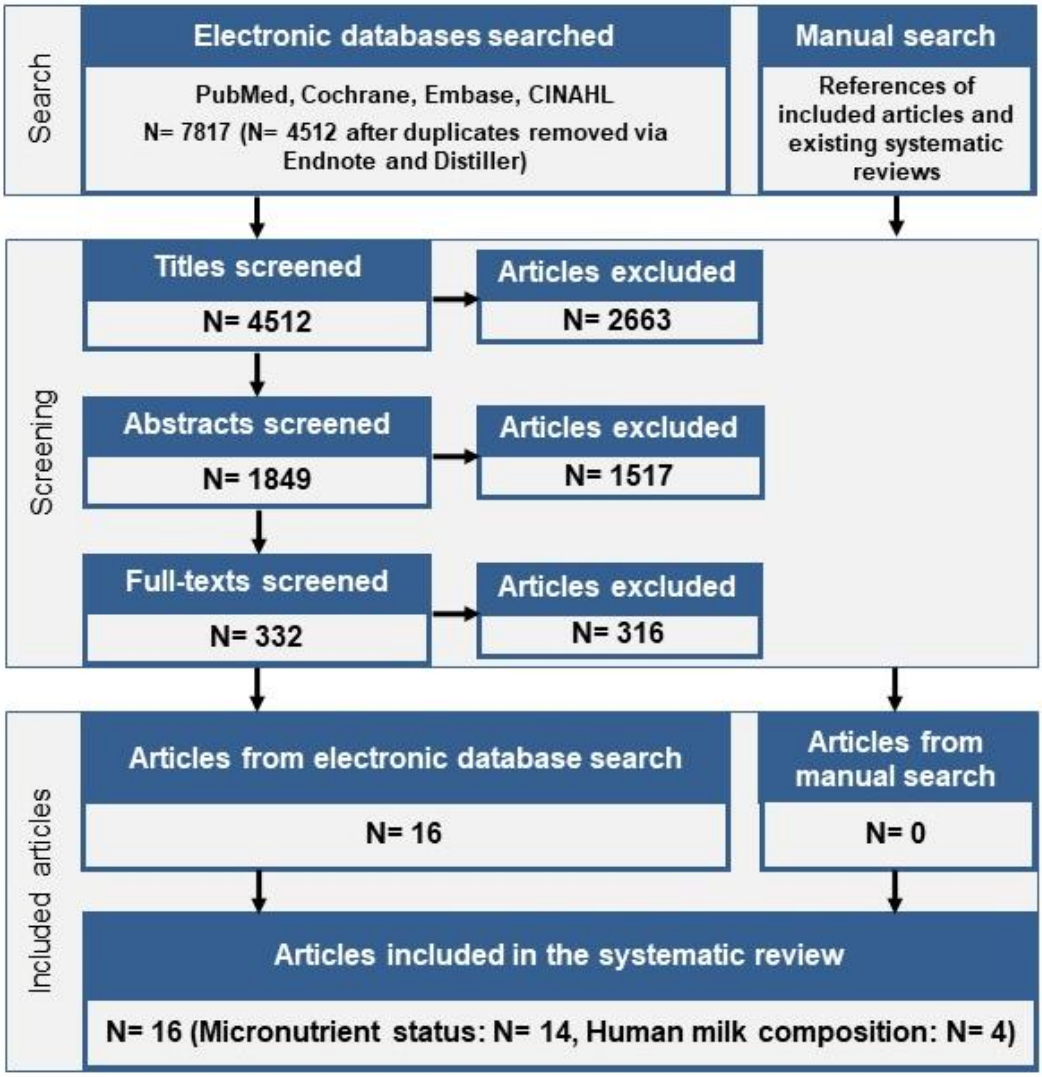
#7 - #6 AND #4

#8 - #7 NOT (MH "Literature Review" OR MH "Meta Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication")
Filters: English Language, Human, Published Date: 20000101 - 20190703

LITERATURE SEARCH AND SCREENING RESULTS

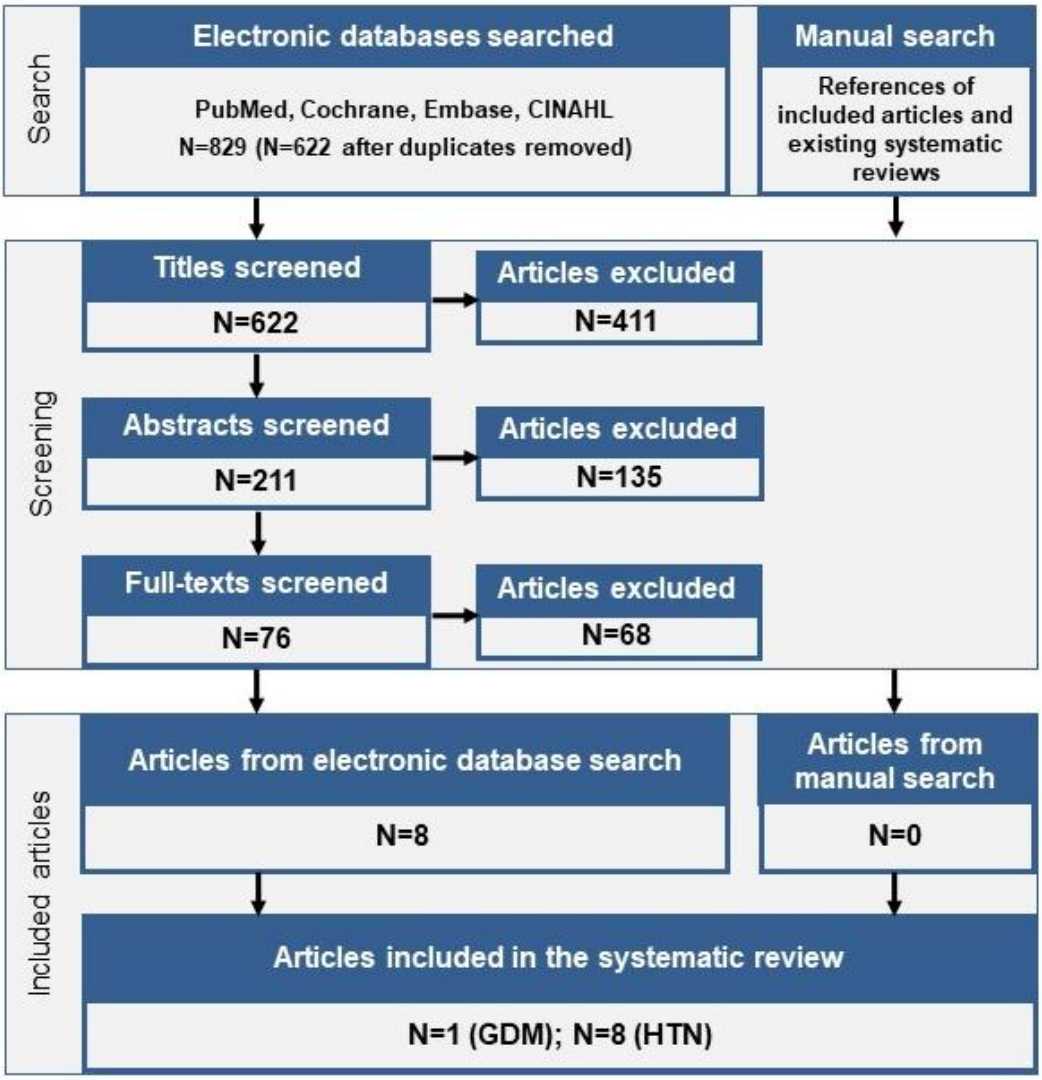
The flow charts (**Figure 6, Figure 7, and Figure 8**) below illustrate the literature search and screening results for articles examining the systematic review questions. One search (**Figure 6**) simultaneously addressed two systematic reviews to answer the following questions: What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and 1) micronutrient status and 2) human milk composition. A second search (**Figure 7**) simultaneously addressed two systematic reviews to answer the following questions: What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and risk of 1) gestational diabetes and 2) hypertensive disorders of pregnancy. A third search (**Figure 8**) addressed the systematic review to answer the question: What is the relationship between folic acid from supplements and/or fortified foods consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. Refer to Excluded Articles (**Table 25, Table 26, and Table 27**) for the rationale for exclusion for each excluded full-text article. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

Figure 6. Flow chart of literature search and screening results: Micronutrient status and Human milk composition[xlix]



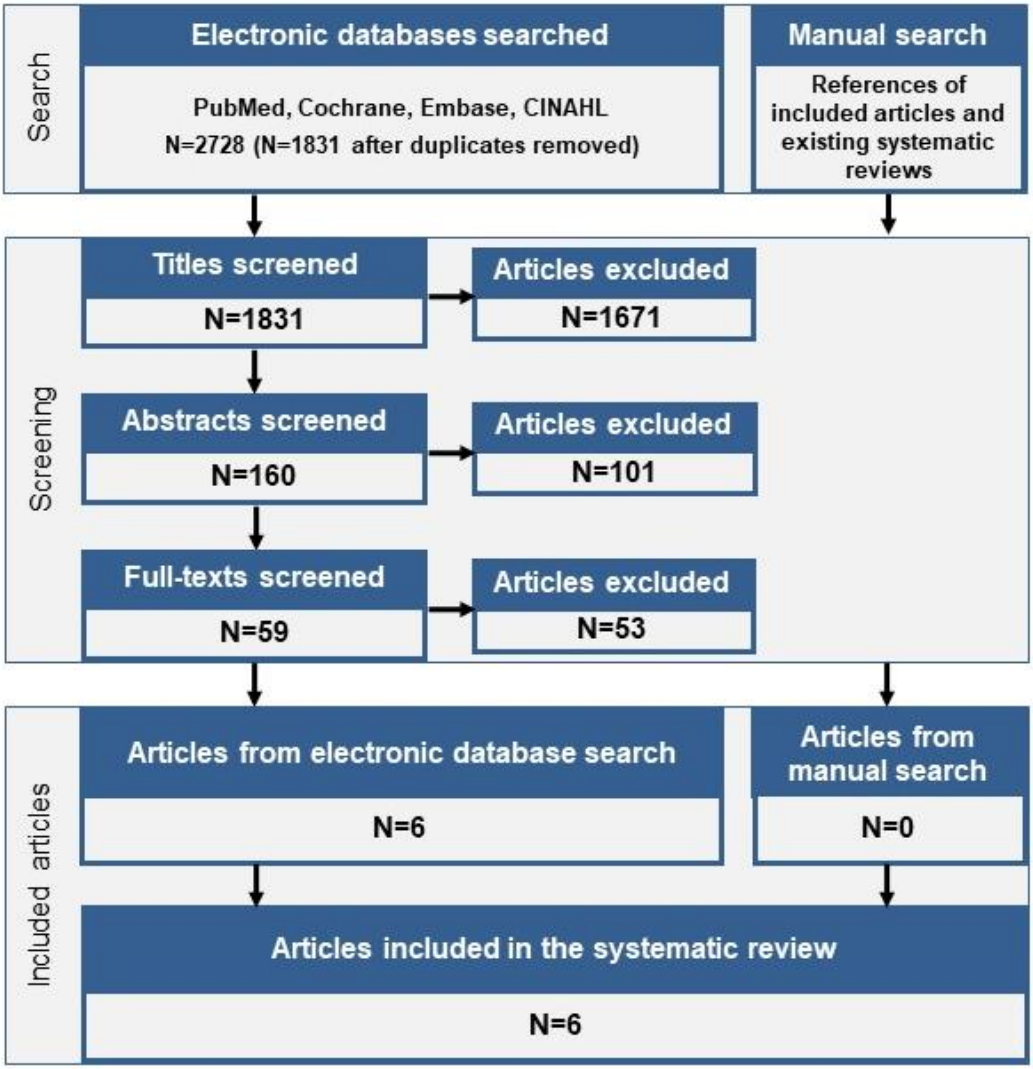
[xlix] Two articles were included in both the review for micronutrient status and the review for human milk composition.

Figure 7. Flow chart of literature search and screening results: Gestational diabetes and Hypertensive disorders of pregnancy[l]



[l] One article was included in both gestational diabetes and hypertensive disorders of pregnancy review.

Figure 8. Flow chart of literature search and screening results: Developmental milestones



Excluded articles

The tables below (**Table 25, Table 26, and Table 27**) list the articles excluded after full-text screening, and include the categories of inclusion and exclusion criteria (see **Table 24**) that studies were excluded based on. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons for exclusion. Information about articles excluded after title and abstract screening is available upon request.

Table 25. Articles excluded after full text screening with rationale for exclusion: Micronutrient status and Human milk composition

	Citation	Rationale
1.	Abdollahi, Z, Elmadfa, I, Djazayery, A, Golalipour, MJ, Sadighi, J, Salehi, F, Sadeghian Sharif, S. Efficacy of flour fortification with folic acid in women of childbearing age in Iran. Ann Nutr Metab. 2011. 58:188-96. doi:10.1159/000329726.	Population
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	Citation	Rationale
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	Citation	Rationale
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	Citation	Rationale
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	Citation	Rationale
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	Citation	Rationale
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	Citation	Rationale
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	Citation	Rationale
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88.	Foreman, JC. Anaemias in pregnancy. Practitioner. 1981. 225:175-84.	Study Design
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91.	Freeman, M, Sosinsky, A, Moustafa, D, Viguera, A, Cohen, L. Supplement use by women during pregnancy: data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Archives of Women's Mental Health. 2016. 19:437-441. doi:10.1007/s00737-015-0586-0.	Outcome
92.	Fruzzetti, F. Beyaz®: An oral contraceptive fortified with folate. Women's Health. 2012. 8:13-19. doi:10.2217/whe.11.68.	Study Design; News/review
93.	Furness, D, Fenech, M, Dekker, G, Khong, YT, Roberts, C, Hague, W. Folate, Vitamin B12, Vitamin B6 and homocysteine: impact on pregnancy outcome. Maternal & Child Nutrition. 2013. 9:155-166. doi:10.1111/j.1740-8709.2011.00364.x.	Study Design
94.	Furness, DL, Yasin, N, Dekker, GA, Thompson, SD, Roberts, CT. Maternal red blood cell folate concentration at 10-12 weeks gestation and pregnancy outcome. Journal of Maternal-Fetal & Neonatal Medicine. 2012. 25:1423-1427. doi:10.3109/14767058.2011.636463.	Study Design
95.	Gadowsky, SL, Gale, K, Wolfe, SA, Jory, J, Gibson, R, O'Connor, DL. Biochemical folate, B12, and iron status of a group of pregnant adolescents accessed through the public health system in southern Ontario. J Adolesc Health. 1995. 16:465-74. doi:10.1016/1054-139x(94)00001-u.	Study Design; Intervention/Exposure
96.	Gaskins, AJ, Yu-Han, C, Williams, PL, Ford, JB, Toth, TL, Hauser, R, Chavarro, JE. Association between serum folate and vitamin B-12 and outcomes of assisted reproductive technologies. American Journal of Clinical Nutrition. 2015. 102:943-950. doi:10.3945/ajcn.115.112185.	Study Design; Outcome; Population

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98.	Gildestad, T, Bjørge, T, Vollset, SE, Klungsøyr, K, Nilsen, RM, Haaland, ØA, Øyen, N. Folic acid supplements and risk for oral clefts in the newborn: a population-based study. British Journal of Nutrition. 2015. 114:1456-1463. doi:10.1017/S0007114515003013.	Outcome
99.	Giugliani, ER, Jorge, SM, Goncalves, AL. Serum vitamin B12 levels in parturients, in the intervillous space of the placenta and in full-term newborns and their interrelationships with folate levels. Am J Clin Nutr. 1985. 41:330-5. doi:10.1093/ajcn/41.2.330.	Intervention/Exposure
100.	Glorimar, R, Pereira, SE, Trugo, NM. Longitudinal change in plasma total homocysteine during pregnancy and postpartum in Brazilian women and its relation with folate status and other factors. Int J Vitam Nutr Res. 2004. 74:95-101. doi:10.1024/0300-9831.74.2.95.	Comparator
101.	Gomber, S, Agarwal, KN, Mahajan, C, Agarwal, N. Impact of daily versus weekly hematinic supplementation on anemia in pregnant women. Indian Pediatr. 2002. 39:339-46.	Comparator; Country
102.	Gómez Roig, MD, Mazarico, E, Ferrero, S, Montejo, R, Ibáñez, L, Grima, F, Vela, A. Differences in dietary and lifestyle habits between pregnant women with small fetuses and appropriate-for-gestational-age fetuses. Journal of Obstetrics & Gynaecology Research. 2017. 43:1145-1151. doi:10.1111/jog.13330.	Outcome
103.	Gringras, M. A comparison of two combined iron-folic acid preparations in the prevention of anaemia in pregnancy. J Int Med Res. 1982. 10:268-70. doi:10.1177/030006058201000413.	Comparator
104.	Gu, Q, Li, Y, Cui, ZL, Luo, XP. Homocysteine, folate, vitamin B(12) and B(6) in mothers of children with neural tube defects in Xinjiang, China. Acta Paediatrica. 2012. 101:e486-90. doi:10.1111/j.1651-2227.2012.02795.x.	Intervention/Exposure
105.	Guerra-Shinohara, EM, Pereira, PM, Kubota, AM, Silva, TA, Reis, JL, Miyashita, GS, D'Almeida, V, Allen, RH, Stabler, SP. Increased MMA concentration and body mass index are associated with spontaneous abortion in Brazilian women: a pilot study. Clin Chim Acta. 2010. 411:423-7. doi:10.1016/j.cca.2009.12.014.	Study Design; Intervention/Exposure
106.	Haggarty, P, Campbell, DM, Duthie, S, Andrews, K, Hoad, G, Piyathilake, C, Fraser, I, McNeill, G. Folic acid use in pregnancy and embryo selection. BJOG: An International Journal of Obstetrics & Gynaecology. 2008. 115:851-856.	Intervention/Exposure; Outcome
107.	Haggarty, P, Hoad, G, Campbell, DM, Horgan, GW, Piyathilake, C, McNeill, G. Folate in pregnancy and imprinted gene and repeat element methylation in the offspring. American Journal of Clinical Nutrition. 2013. 97:94-99. doi:10.3945/ajcn.112.042572.	Outcome; Exposure & outcome measured at same time
108.	Haggarty, P, McCallum, H, McBain, H, Andrews, K, Duthie, S, McNeill, G, Templeton, A, Haites, N, Campbell, D, Bhattacharya, S. Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet. 2006. 367 North American Edition:1513-1519.	Study Design; Comparator

	Citation	Rationale
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110.	Hartman, BA, Fazili, Z, Pfeiffer, CM, O'Connor, DL. Neither folic acid supplementation nor pregnancy affects the distribution of folate forms in the red blood cells of women. Journal of Nutrition. 2014. 144:1364-1369. doi:10.3945/jn.113.189233.	Study Design; Comparator
111.	Haruna, M, Shiraishi, M, Matsuzaki, M, Yatsuki, Y, Yeo, SA. Effect of tailored dietary guidance for pregnant women on nutritional status: A double-cohort study. Maternal & Child Nutrition. 2017. 13:n/a-N.PAG. doi:10.1111/mcn.12391.	Intervention/Exposure; Comparator
112.	Hashemi, M, Heshmat-Ghahdarijani, K, Zarean, E, Baktash, F, Mortazavi, ZS. Evaluation of the effect of high-dose folic acid on endothelial dysfunction in pre-eclamptic patients: A randomized clinical trial. Journal of Research in Medical Sciences. 2016. 21.	Outcome
113.	Hauser, GA. Vitamin requirements in human pregnancy. Int J Vitam Nutr Res Suppl. 1985. 27:207-12.	Comparator
114.	Hay, G, Clausen, T, Whitelaw, A, Trygg, K, Johnston, C, Henriksen, T, Refsum, H. Maternal folate and cobalamin status predicts vitamin status in newborns and 6-month-old infants. Journal of Nutrition. 2010. 140:557-564. doi:10.3945/jn.109.117424.	Study Design; Outcome
115.	Heppe, DHM, Medina-Gomez, C, Hofman, A, Franco, OH, Rivadeneira, F, Jaddoe, VWVW. Maternal first-trimester diet and childhood bone mass: the Generation R Study. American Journal of Clinical Nutrition. 2013. 98:224-232. doi:10.3945/ajcn.112.051052.	Intervention/Exposure; Outcome
116.	Hess, SY, Zimmermann, MB, Brogli, S, Hurrell, RF. A national survey of iron and folate status in pregnant women in Switzerland. Int J Vitam Nutr Res. 2001. 71:268-73. doi:10.1024/0300-9831.71.5.268.	Study Design; Intervention/Exposure; Comparator
117.	Hibbard, BM. Iron and folate supplements during pregnancy: supplementation is valuable only in selected patients. Bmj. 1988. 297:1324, 1326. doi:10.1136/bmj.297.6659.1324.	Outcome; Not primary data
118.	Higgins, JR, Quinlivan, EP, McPartlin, J, Scott, JM, Weir, DG, Darling, MR. The relationship between increased folate catabolism and the increased requirement for folate in pregnancy. Bjog. 2000. 107:1149-54.	Intervention/Exposure
119.	Hindmarsh, PC, Geary, MPP, Rodeck, CH, Jackson, MR, Kingdom, JCP, Hindmarsh, PC, Geary, MP, Rodeck, CH, Jackson, MR, Kingdom, JC. Effect of early maternal iron stores on placental weight and structure. Lancet. 2000. 356 North American Edition:719-723.	Study Design; Intervention/Exposure
120.	Hininger, I, Favier, M, Arnaud, J, Faure, H, Thoulon, JM, Hariveau, E, Favier, A, Roussel, AM. Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. Eur J Clin Nutr. 2004. 58:52-9. doi:10.1038/sj.ejcn.1601745.	Comparator

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122.	House, JD, March, SB, Ratnam, S, Crowley, M, Friel, JK, House, JamesD, March, SandraB, Ratnam, Msc Sam, Crowley, Marilyn, Friel, JamesK. Improvements in the status of folate and cobalamin in pregnant Newfoundland women are consistent with observed reductions in the incidence of neural tube defects. Canadian Journal of Public Health. 2006. 97:132-135.	Study Design
123.	Hure, A, Collins, C, Smith, R. A Longitudinal Study of Maternal Folate and Vitamin B12 Status in Pregnancy and Postpartum, with the Same Infant Markers at 6 Months of Age. Maternal & Child Health Journal. 2012. 16:792-801. doi:10.1007/s10995-011-0782-0.	Intervention/Exposure; Comparator
124.	Hursthouse, NA, Gray, AR, Miller, JC, Rose, MC, Houghton, LA. Folate status of reproductive age women and neural tube defect risk: the effect of long-term folic acid supplementation at doses of 140 microg and 400 microg per day. Nutrients. 2011. 3:49-62. doi:10.3390/nu3010049.	Population
125.	Hursthouse, NA, Gray, AR, Miller, JC, Rose, MC, Houghton, LA. Folate status of reproductive age women and neural tube defect risk: The effect of long-term folic acid supplementation at doses of 140 µg and 400 µg per day. Nutrients. 2011. 3:49-62. doi:10.3390/nu3010049.	Population
126.	Iron/folate for iron deficiency anaemia in pregnancy. Australian journal of pharmacy. 2008. 89:76-.	Study Design; Not peer-reviewed
127.	Jackson, E, Mathur, K. Adolescent pregnancy: effects of nutrients on hematocrit and birth weight in Orangeburg County. J S C Med Assoc. 1991. 87:8-11.	Study Design; Intervention/Exposure; Comparator
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129.	Jain, R, Acharya, AS. Supplemental folic acid in pregnancy and childhood asthma. National Medical Journal of India. 2010. 23:351-352.	Study Design; Outcome; Summary/Commentary
130.	Jans, G, Matthys, C, Bel, S, Ameye, L, Lannoo, M, Van der Schueren, B, Dillemans, B, Lemmens, L, Saey, J-P, van Nieuwenhove, Y, Grandjean, P, De Becker, B, Logghe, H, Coppens, M, Roelens, K, Loccufier, A, Verhaeghe, J, Devlieger, R. AURORA: bariatric surgery registration in women of reproductive age - a multicenter prospective cohort study. BMC Pregnancy & Childbirth. 2016. 16:1-11. doi:10.1186/s12884-016-0992-y.	Study Design
131.	Jarvenpaa, J, Schwab, U, Lappalainen, T, Pakkila, M, Niskanen, L, Punnonen, K. Mineral water fortified with folic acid and vitamins B6, B12, D and calcium improves folate status and decreases plasma homocysteine concentration in pregnant women. 35th nordic congress of obstetrics and gynecology; 2006 may 23-25; goteburg, Sweden. 2008. 55.	Abstract

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133.	Jiang, HL, Cao, LQ, Chen, HY. Blood folic acid, vitamin B12, and homocysteine levels in pregnant women with fetal growth restriction. Genet Mol Res. 2016. 15. doi:10.4238/gmr15048890.	Intervention/Exposure
134.	Joelson, DW, Fiebig, EW, Wu, AH. Diminished need for folate measurements among indigent populations in the post folic acid supplementation era. Arch Pathol Lab Med. 2007. 131:477-80. doi:10.1043/1543-2165(2007)131[477:Dnffma]2.0.Co;2.	Population
135.	Jwa, SC, Ogawa, K, Kobayashi, M, Morisaki, N, Sago, H, Fujiwara, T. Validation of a food-frequency questionnaire for assessing vitamin intake of Japanese women in early and late pregnancy with and without nausea and vomiting. J Nutr Sci. 2016. 5:e27. doi:10.1017/jns.2016.14.	Comparator
136.	Kalem, P, Benli, AR, Koroglu, M, Benli, NC, Koyuncu, M, Cesur, O, Dane, PBK. The effect of ferritin, vitamin B12 and folic acid on pregnancy outcomes. International Journal of Clinical and Experimental Medicine. 2016. 9:22413-22417.	Intervention/Exposure; Comparator
137.	Kang, Y, Dang, S, Zeng, L, Wang, D, Li, Q, Wang, J, Ouzhu, L, Yan, H. Multi-micronutrient supplementation during pregnancy for prevention of maternal anaemia and adverse birth outcomes in a high-altitude area: a prospective cohort study in rural Tibet of China. British Journal of Nutrition. 2017. 118:431-440. doi:10.1017/S000711451700229X.	Study Design; Comparator
138.	Kaplan, JS, Iqbal, S, England, BG, Zawacki, CM, Herman, WH. Is pregnancy in diabetic women associated with folate deficiency? Diabetes Care. 1999. 22:1017-21. doi:10.2337/diacare.22.7.1017.	Intervention/Exposure; Comparator
139.	Karabulut, A, Şevket, O, Acun, A. Iron, folate and vitamin B12 levels in first trimester pregnancies in the Southwest region of Turkey. Journal of the Turkish-German Gynecological Association. 2011. 12:153-156. doi:10.5152/jtgga.2011.36.	Intervention/Exposure
140.	Karra, MV, Udipi, SA, Kirksey, A, Roepke, JL. Changes in specific nutrients in breast milk during extended lactation. Am J Clin Nutr. 1986. 43:495-503. doi:10.1093/ajcn/43.4.495.	Intervention/Exposure; Comparator
141.	Khambalia, A, Latulippe, ME, Campos, C, Merlos, C, Villalpando, S, Picciano, MF, O'Connor D, L. Milk folate secretion is not impaired during iron deficiency in humans. J Nutr. 2006. 136:2617-24. doi:10.1093/jn/136.10.2617.	Comparator
142.	Kharb, S, Aggarwal, D, Bala, J, Nanda, S. Evaluation of Homocysteine, Vitamin B12 and Folic Acid Levels During all the Trimesters in Pregnant and Preeclamptic Womens. Curr Hypertens Rev. 2016. 12:234-238. doi:10.2174/1573402112666161010151632.	Intervention/Exposure; Country
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144.	Kiefte-de Jong, JC, Timmermans, S, Jaddoe, VW, Hofman, A, Tiemeier, H, Steegers, EA, de Jongste, JC, Moll, HA. High circulating folate and vitamin B-12 concentrations in women during pregnancy are associated with increased prevalence of atopic dermatitis in their offspring. Journal of Nutrition. 2012. 142:731-738.	Study Design
145.	Kilbride, J, Baker, TG, Parapia, LA, Khoury, SA, Kilbride, J, Baker, TG, Parapia, LA, Khoury, SA. Iron status, serum folate and B(12) values in pregnancy and postpartum: report from a study in Jordan. Annals of Saudi Medicine. 2000. 20:371-376.	Intervention/Exposure; Country
146.	Koc, A, Kocyigit, A, Soran, M, Demir, N, Sevinc, E, Erel, O, Mil, Z. High frequency of maternal vitamin B12 deficiency as an important cause of infantile vitamin B12 deficiency in Sanliurfa province of Turkey. European Journal of Nutrition. 2006. 45:291-297.	Intervention/Exposure
147.	Kocic, G, Bjelakovic, L, Bjelakovic, B, Jevtoci-Stoimenov, T, Sokolovic, D, Cvetkovic, T, Kocic, H, Stojanovic, S, Langerholc, T, Jonovic, M. Impact of Folic Acid Supplementation on Single- and Double-Stranded RNA Degradation in Human Colostrum and Mature Milk. Journal of Medicinal Food. 2014. 17:804-809. doi:10.1089/jmf.2013.0093.	Outcome
148.	Kocylowski, Rafal, Grzesiak, Mariusz, Gaj, Zuzanna, Lorenc, Wiktor, Bakinowska, Ewa, Barałkiewicz, Danuta, von Kaisenberg, ConstantinS, Lamers, Yvonne, Suliburska, Joanna. Associations between the Level of Trace Elements and Minerals and Folate in Maternal Serum and Amniotic Fluid and Congenital Abnormalities. Nutrients. 2019. 11:328. doi:10.3390/nu11020328.	Intervention/Exposure
149.	Koenig, MD, McFarlin, BL, Steffen, AD, Tussing-Humphreys, L, Giurgescu, C, Engeland, CG, Kominiarek, MA, Ciezczak-Karpiel, C, O'Brien, WD, White-Traut, R. Decreased Nutrient Intake Is Associated With Premature Cervical Remodeling. JOGNN: Journal of Obstetric, Gynecologic & Neonatal Nursing. 2017. 46:123-134. doi:10.1016/j.jogn.2016.08.006.	Intervention/Exposure; Outcome
150.	Kokanali, MK, Ozturkkan, D, Unsal, N, Moroy, P, Gungor, T, Mollamahmutoglu, L. Plasma homocysteine, vitamin B12 and folate levels in hydatidiform moles and histopathological subtypes. Arch Gynecol Obstet. 2008. 278:531-4. doi:10.1007/s00404-008-0637-0.	Intervention/Exposure; Comparator
151.	Koren, G. Preconceptional folate and neural tube defects: Time for rethinking. Canadian Journal of Public Health. 1993. 84:207-208.	Study Design; Not primary data
152.	Korkmaz, V, Ozkaya, E, Seven, BY, Duzguner, S, Karsli, MF, Kucukozkan, T. Comparison of oxidative stress in pregnancies with and without first trimester iron supplement: a randomized double-blind controlled trial. Journal of Maternal-Fetal & Neonatal Medicine. 2014. 27:1535-1538. doi:10.3109/14767058.2013.863869.	Outcome
153.	Kösüs, N, Kösüs, A, Hizli, D, Bitirgen, EÜ, Turhan, NÖ. Can serum ferritin, vitamin B(12) and folic acid levels affect serum screening tests during pregnancy? Journal of Maternal-Fetal & Neonatal Medicine. 2012. 25:1674-1677. doi:10.3109/14767058.2012.657276.	Intervention/Exposure
154.	Krauss-Etschmann, S, Shadid, R, Campoy, C, Hoster, E, Demmelmair, H, Jiménez, M, Gil, A, Rivero, M, Veszprémi, B, Decsi, T, Koletzko, BV. Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. American Journal of Clinical Nutrition. 2007. 85:1392-1400.	Study Design; Outcome

	Citation	Rationale
155.	La Merrill, M, Torres-Sánchez, L, Ruiz-Ramos, R, López-Carrillo, L, Cebrián, ME, Chen, J, La Merrill, Michele, Torres-Sánchez, Luisa, Ruiz-Ramos, Rubén, López-Carrillo, Lizbeth, Cebrián, MarianoE, Chen, Jia. The association between first trimester micronutrient intake, MTHFR genotypes, and global DNA methylation in pregnant women. Journal of Maternal-Fetal & Neonatal Medicine. 2012. 25:133-137. doi:10.3109/14767058.2011.564242.	Intervention/Exposure
156.	Lacasaña, M, Blanco-Muñoz, J, Borja-Aburto, VH, Aguilar-Garduño, C, Rodríguez-Barranco, M, Sierra-Ramirez, JA, Galaviz-Hernandez, C, Gonzalez-Alzaga, B, Garcia-Cavazos, R. Effect on risk of anencephaly of gene-nutrient interactions between methylenetetrahydrofolate reductase C677T polymorphism and maternal folate, vitamin B12 and homocysteine profile. Public Health Nutrition. 2012. 15:1419-1428. doi:10.1017/S136898001100334X.	Intervention/Exposure; Outcome
157.	Lamers, Y, Prinz-Langenohl, R, Moser, R, Pietrzik, K. Supplementation with [6S]-5-methyltetrahydrofolate or folic acid equally reduces plasma total homocysteine concentrations in healthy women. American Journal of Clinical Nutrition. 2004. 79:473-478.	Population
158.	Lawrence, JM, Watkins, ML, Chiu, V, Erickson, JD, Petitti, DB. Do racial and ethnic differences in serum folate values exist after food fortification with folic acid? American Journal of Obstetrics & Gynecology. 2006. 194:520-526.	Study Design
159.	Lehti, KK. Iron, folic acid and zinc intakes and status of low socio-economic pregnant and lactating Amazonian women. Eur J Clin Nutr. 1989. 43:505-13.	Intervention/Exposure; Country
160.	Li, C, Zeng, L, Wang, D, Yang, W, Dang, S, Zhou, J, Yan, H. Prenatal Micronutrient Supplementation Is Not Associated with Intellectual Development of Young School-Aged Children. J Nutr. 2015. 145:1844-9. doi:10.3945/jn.114.207795.	Outcome; Country
161.	Li, X, Jiang, J, Xu, M, Xu, M, Yang, Y, Lu, W, Yu, X, Ma, J, Pan, J. Individualized supplementation of folic acid according to polymorphisms of methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR) reduced pregnant complications. Gynecol Obstet Invest. 2015. 79:107-12. doi:10.1159/000367656.	Outcome
162.	Li, X, Li, S, Mu, D, Liu, Z, Li, Y, Lin, Y, Chen, X, You, F, Li, N, Deng, K, Deng, Y, Wang, Y, Zhu, J. The association between periconceptional folic acid supplementation and congenital heart defects: A case-control study in China. Preventive Medicine. 2013. 56:385-389. doi:10.1016/j.ypmed.2013.02.019.	Outcome
163.	Li, Z, Mei, Z, Zhang, L, Li, H, Zhang, Y, Li, N, Ye, R, Ren, A, Liu, J-M, Serdula, MK. Effects of Prenatal Micronutrient Supplementation on Spontaneous Preterm Birth: A Double-Blind Randomized Controlled Trial in China. American Journal of Epidemiology. 2017. 186:318-325. doi:10.1093/aje/kwx094.	Outcome; Country
164.	Li, Z, Ye, R, Zhang, L, Li, H, Liu, J, Ren, A. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension (0194911X). 2013. 61:873-879. doi:10.1161/HYPERTENSIONAHA.111.00230.	Outcome; Country

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165.	Li, Z, Ye, R, Zhang, L, Li, H, Liu, J, Ren, A. Periconceptional folic acid supplementation and the risk of preterm births in China: a large prospective cohort study. International Journal of Epidemiology. 2014. 43:1132-1139. doi:10.1093/ije/dyu020.	Outcome
166.	Little, J, Gilmour, M, Mossey, PA, FitzPatrick, D, Cardy, A, Clayton-Smith, J, Hill, A, Duthie, SJ, Fryer, AE, Molloy, AM, Scott, JM. Folate and clefts of the lip and palate -- a U.K.-based case-control study: part II: biochemical and genetic analysis. Cleft Palate-Craniofacial Journal. 2008. 45:428-438.	Study Design; Comparator
167.	Liu, Jian-Meng, Mei, Zuguo, Ye, Rongwei, Serdula, MaryK, Ren, Aiguo, Cogswell, MaryE. Micronutrient supplementation and pregnancy outcomes: double-blind randomized controlled trial in china. JAMA Internal Medicine. 2013. 173:276-282. doi:10.1001/jamainternmed.2013.1632.	Intervention/Exposure; Outcome; Country
168.	Liu, S, West, R, Randell, E, Longerich, L, O'Connor, KS, Scott, H, Crowley, M, Lam, A, Prabhakaran, V, McCourt, C. A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. BMC Pregnancy and Childbirth. 2004. 4. doi:10.1186/1471-2393-4-20.	Outcome; Population
169.	Livock, M, Anderson, PJ, Lewis, S, Bowden, S, Muggli, E, Halliday, J. Maternal micronutrient consumption periconceptionally and during pregnancy: a prospective cohort study. Public Health Nutrition. 2017. 20:294-304. doi:10.1017/S1368980016002019.	Outcome
170.	Looman, M, Geelen, A, Samlal, RAK, Heijligenberg, R, Gunnewiek, JMTK, Balvers, MGJ, Wijnberger, LDE, Brouwer-Brolsma, EM, Feskens, EJM. Changes in Micronutrient Intake and Status, Diet Quality and Glucose Tolerance from Preconception to the Second Trimester of Pregnancy. Nutrients. 2019. 11:460. doi:10.3390/nu11020460.	Study Design; Comparator
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	Citation	Rationale
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256.	Smith, AM, Picciano, MF, Deering, RH. Folate supplementation during lactation: maternal folate status, human milk folate content, and their relationship to infant folate status. J Pediatr Gastroenterol Nutr. 1983. 2:622-8.	Comparator
257.	Sneed, SM, Zane, C, Thomas, MR. The effects of ascorbic acid, vitamin B6, vitamin B12, and folic acid supplementation on the breast milk and maternal nutritional status of low socioeconomic lactating women. Am J Clin Nutr. 1981. 34:1338-46. doi:10.1093/ajcn/34.7.1338.	Intervention/Exposure; Comparator
258.	Solé-Navais, P, Salat-Batlle, J, Cavallé-Busquets, P, Fernandez-Ballart, J, Ueland, PM, Ballesteros, M, Ornosa-Martín, G, Inglès-Puig, M, Colomina, JM, Murphy, MM. Early pregnancy folate-cobalamin interactions and their effects on cobalamin status and hematologic variables throughout pregnancy. American Journal of Clinical Nutrition. 2018. 107:173-182. doi:10.1093/ajcn/nqx041.	Intervention/Exposure; Comparator

	Citation	Rationale
259.	Srisupandit, S, Pootrakul, P, Areekul, S, Neungton, S, Mokkaves, J, Kiriwat, O, Kanokpongsukdi, S. A prophylactic supplementation of iron and folate in pregnancy. Southeast Asian J Trop Med Public Health. 1983. 14:317-23.	Country
260.	Stamm, RA, March, KM, Karakochuk, CD, Gray, AR, Brown, RC, Green, TJ, Houghton, LA. Lactating Canadian Women Consuming 1000 microg Folic Acid Daily Have High Circulating Serum Folic Acid Above a Threshold Concentration of Serum Total Folate. J Nutr. 2018. 148:1103-1108. doi:10.1093/jn/nxy070.	Comparator
261.	Stamm, RA, March, KM, Karakochuk, CD, Gray, AR, Brown, RC, Green, TJ, Houghton, LA. Lactating Canadian women consuming 1000 µg folic acid daily have high serum folic acid above a threshold concentration of serum total folate. Journal of Nutrition. 2018. 148:1103-1108. doi:10.1093/jn/nxy070.	Intervention/Exposure; Comparator
262.	Stamm, RA, March, KM, Karakochuk, CD, Gray, AR, Brown, RC, Green, TJ, Houghton, LA. Lactating Canadian Women Consuming 1000 µg Folic Acid Daily Have High Circulating Serum Folic Acid Above a Threshold Concentration of Serum Total Folate. Journal of Nutrition. 2018. 148:1130-1108. doi:10.1093/jn/nxy070.	Intervention/Exposure; Comparator
263.	Stang, J, Brown, J, Jacobs, D, Jr. Effects of iron and folic acid supplements on serum zinc levels among a cohort of pregnant women. Topics in Clinical Nutrition. 2002. 17:15-26.	Outcome
264.	Steegers-Theunissen, RP, Steegers, EA, de Boer, R, Thomas, CM, Kloosterman, MD, Eskes, TK. Elevated folate levels in amniotic fluid after oral supplementation. Eur J Obstet Gynecol Reprod Biol. 1990. 36:283-91.	Intervention/Exposure; Comparator
265.	Stingone, JA, Luben, TJ, Carmichael, SL, Aylsworth, AS, Botto, LD, Correa, A, Gilboa, SM, Langlois, PH, Nembhard, WN, Richmond-Bryant, J, Shaw, GM, Olshan, AF. Maternal Exposure to Nitrogen Dioxide, Intake of Methyl Nutrients, and Congenital Heart Defects in Offspring. American Journal of Epidemiology. 2017. 186:719-729. doi:10.1093/aje/kwx139.	Outcome
266.	Suarez, L, Hendricks, K, Felkner, M, Gunter, E. Maternal serum B12 levels and risk for neural tube defects in a Texas-Mexico border population. Annals of Epidemiology. 2003. 13:81-88.	Intervention/Exposure; Comparator
267.	Sufang, W, Xing, G, Beibei, Z, Yujie, X, Kun, H, Erigene, R, Leijing, M, Sanhuan, H, Shuangqin, Y, Fangbiao, T. Maternal Continuing Folic Acid Supplementation after the First Trimester of Pregnancy Increased the Risk of Large-for-Gestational-Age Birth: A Population-Based Birth Cohort Study. Nutrients. 2016. 8:493. doi:10.3390/nu8080493.	Outcome
268.	Sun, YY, Ma, AG, Yang, F, Zhang, FZ, Luo, YB, Jiang, DC, Han, XX, Liang, H. A combination of iron and retinol supplementation benefits iron status, IL-2 level and lymphocyte proliferation in anemic pregnant women. Asia Pacific Journal of Clinical Nutrition. 2010. 19:513-519.	Comparator; Outcome; Country
269.	Surén, P, Roth, C, Bresnahan, M, Haugen, M, Hornig, M, Hirtz, D, Lie, KK, Lipkin, WI, Magnus, P, Reichborn-Kjennerud, T, Schjølberg, S, Smith, GD, Øyen, A-S, Susser, E, Stoltenberg, C. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA: Journal of the American Medical Association. 2013. 309:570-577. doi:10.1001/jama.2012.155925.	Outcome

	Citation	Rationale
270.	Sweeney, MR, Staines, A, Daly, L, Traynor, A, Daly, S, Bailey, SW, Alverson, PB, Ayling, JE, Scott, JM. Persistent circulating unmetabolised folic acid in a setting of liberal voluntary folic acid fortification. Implications for further mandatory fortification? BMC Public Health. 2009. 9:295-295. doi:10.1186/1471-2458-9-295.	Study Design
271.	Taghizadeh, M, Samimi, M, Tabassi, Z, Heidarzadeh, Z, Asemi, Z. Effect of multivitamin-mineral versus multivitamin supplementation on maternal, newborns' biochemical indicators and birth size: A double-blind randomized clinical trial. Oman Medical Journal. 2014. 29:123-129. doi:10.5001/omj.2014.30.	Intervention/Exposure; Comparator
272.	Takimoto, H, Hayashi, F, Kusama, K, Kato, N, Yoshiike, N, Toba, M, Ishibashi, T, Miyasaka, N, Kubota, T. Elevated maternal serum folate in the third trimester and reduced fetal growth: a longitudinal study. J Nutr Sci Vitaminol (Tokyo). 2011. 57:130-7.	Study Design
273.	Takimoto, H, Mito, N, Umegaki, K, Ishiwaki, A, Kusama, K, Abe, S, Yamawaki, M, Fukuoka, H, Ohta, C, Yoshiike, N. Relationship between dietary folate intakes, maternal plasma total homocysteine and B-vitamins during pregnancy and fetal growth in Japan. European Journal of Nutrition. 2007. 46:300-306.	Intervention/Exposure; Comparator; Outcome
274.	Tamura, T, Goldenberg, RL, Freeberg, LE, Cliver, SP, Cutter, GR, Hoffman, HJ. Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. Am J Clin Nutr. 1992. 56:365-70. doi:10.1093/ajcn/56.2.365.	Intervention/Exposure
275.	Tamura, T, Goldenberg, RL, Johnston, KE, Cliver, SP, Hoffman, HJ. Serum concentrations of zinc, folate, vitamins A and E, and proteins, and their relationships to pregnancy outcome. Acta Obstet Gynecol Scand Suppl. 1997. 165:63-70.	Intervention/Exposure; Comparator
276.	Taylor, TN, Farkouh, RA, Graham, JB, Colligs, A, Lindemann, M, Lynen, R, Candrilli, SD. Potential reduction in neural tube defects associated with use of Metafolin-fortified oral contraceptives in the United States. American Journal of Obstetrics & Gynecology. 2011. 205:460.e1-8.	Study Design; Human; Mathematical modeling
277.	Tchernia, G, Blot, I, Rey, A, Kaltwasser, JP, Zittoun, J, Papiernik, E. Maternal folate status, birthweight and gestational age. Dev Pharmacol Ther. 1982. 4 Suppl:58-65.	Comparator; Outcome
278.	Thomas, MR, Sneed, SM, Wei, C, Nail, PA, Wilson, M, Sprinkle, EE, 3rd. The effects of vitamin C, vitamin B6, vitamin B12, folic acid, riboflavin, and thiamin on the breast milk and maternal status of well-nourished women at 6 months postpartum. Am J Clin Nutr. 1980. 33:2151-6. doi:10.1093/ajcn/33.10.2151.	Comparator
279.	Titaley, CR, Dibley, MJ, Roberts, CL, Agho, K. Combined iron/folic acid supplements and malaria prophylaxis reduce neonatal mortality in 19 sub-Saharan African countries. American Journal of Clinical Nutrition. 2010. 92:235-243. doi:10.3945/ajcn.2009.29093.	Country
280.	Tiwari, AKM, Mahdi, AA, Mishra, S. Study on Impact of Iron and Folic Acid on the Plasma Trace Minerals in Pregnant Anemic Women. Indian J Clin Biochem. 2018. 33:31-37. doi:10.1007/s12291-017-0653-6.	Intervention/Exposure; Country
281.	Tomedi, LE, Chang, C-CH, Newby, PK, Evans, RW, Luther, JF, Wisner, KL, Bodnar, LM, Newby, PK. Pre-pregnancy obesity and maternal nutritional biomarker status during pregnancy: a factor analysis. Public Health Nutrition. 2013. 16:1414-1418. doi:10.1017/S1368980013000736.	Study Design; Intervention/Exposure

	Citation	Rationale
282.	Trugo, NMF, Donangelo, CM, Seyfarth, BSP, Henriques, C, Andrade, LP. Folate and iron status of non-anemic women during pregnancy: Effect of routine folate and iron supplementation and relation of erythrocyte folate with iron stores. Nutrition Research. 1996. 16:1267-1276. doi:10.1016/0271-5317(96)00136-4.	Country
283.	Tserga, A, Binder, AM, Michels, KB. Impact of folic acid intake during pregnancy on genomic imprinting of IGF2/H19 and 1-carbon metabolism. Faseb j. 2017. 31:5149-5158. doi:10.1096/fj.201601214RR.	Study Design; Outcome
284.	Udipi, SA, Kirksey, A, West, K, Giacoia, G. Vitamin B6, vitamin C and folacin levels in milk from mothers of term and preterm infants during the neonatal period. Am J Clin Nutr. 1985. 42:522-30. doi:10.1093/ajcn/42.3.522.	Intervention/Exposure; Comparator
285.	Valera-Gran, D, Navarrete-Munoz, EM, Garcia de la Hera, M, Fernandez-Somoano, A, Tardon, A, Ibarluzea, J, Balluerka, N, Murcia, M, Gonzalez-Safont, L, Romaguera, D, Julvez, J, Vioque, J. Effect of maternal high dosages of folic acid supplements on neurocognitive development in children at 4-5 y of age: the prospective birth cohort Infancia y Medio Ambiente (INMA) study. Am J Clin Nutr. 2017. 106:878-887. doi:10.3945/ajcn.117.152769.	Outcome
286.	van den Hil, LCL, Taal, HR, de Jonge, LL, Heppe, DHM, Steegers, EAP, Hofman, A, van der Heijden, AJ, Jaddoe, VWV. Maternal first-trimester dietary intake and childhood blood pressure: the Generation R Study. British Journal of Nutrition. 2013. 110:1454-1464. doi:10.1017/S0007114513000676.	Study Design; Outcome
287.	Van Der Woude, DAA, De Vries, J, Van Wijk, EM, Verzijl, JM, Pijnenborg, JMA. A randomized controlled trial examining the addition of folic acid to iron supplementation in the treatment of postpartum anemia. International Journal of Gynecology & Obstetrics. 2014. 126:101-105. doi:10.1016/j.ijgo.2014.02.013.	Population
288.	van Lee, L, Tint, MT, Aris, IM, Quah, PL, Fortier, MV, Lee, YS, Yap, FK, Saw, SM, Godfrey, KM, Gluckman, PD, Chong, YS, Kramer, MS, Chong, MF-F. Prospective associations of maternal betaine status with offspring weight and body composition at birth: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study. American Journal of Clinical Nutrition. 2016. 104:1327-1333. doi:10.3945/ajcn.116.138818.	Intervention/Exposure; Outcome
289.	Vanderlelie, J, Scott, R, Shibl, R, Lewkowicz, J, Perkins, A, Scuffham, PA. First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women. Maternal & Child Nutrition. 2016. 12:339-348. doi:10.1111/mcn.12133.	Outcome
290.	Varea, A, Malpeli, A, Disalvo, L, Apezteguia, M, Falivene, M, Ferrari, G, Pereyras, S, Carmuega, E, Etchegoyen, G, Vojkovic, M, Gonzalez, HF. Evaluation of the impact of a food program on the micronutrient nutritional status of Argentinean lactating mothers. Biol Trace Elem Res. 2012. 150:103-8. doi:10.1007/s12011-012-9512-8.	Intervention/Exposure; Comparator
291.	Venn, BJ, Green, TJ, Moser, R, McKenzie, JE, Murray Skeaff, C, Mann, J. Increases in blood folate indices are similar in women of childbearing age supplemented with [6S]-5-methyltetrahydrofolate and folic acid. Journal of Nutrition. 2002. 132:3353-3355.	Population

	Citation	Rationale
292.	Verkleij-Hagoort, AC, de Vries, JHM, Stegers, MPG, Lindemans, J, Ursem, NTC, Steegers-Theunissen, RPM. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. European Journal of Clinical Nutrition. 2007. 61:610-615.	Intervention/Exposure; Comparator
293.	Verkleij-Hagoort, AC, de Vries, JHM, Ursem, NTC, de Jonge, R, Hop, WCJ, Steegers-Theunissen, RPM. Dietary intake of B-vitamins in mothers born a child with a congenital heart defect. European Journal of Nutrition. 2006. 45:478-486.	Study Design; Population
294.	Villalpando, S, Latulippe, ME, Rosas, G, Irurita, MJ, Picciano, MF, O'Connor, DL. Milk folate but not milk iron concentrations may be inadequate for some infants in a rural farming community in San Mateo, Capulhuac, Mexico. American Journal of Clinical Nutrition. 2003. 78:782-789.	Intervention/Exposure
295.	Villamor, E, Rifas-Shiman, SL, Gillman, MW, Oken, E, Villamor, E, Rifas-Shiman, SL, Gillman, MW, Oken, E. Maternal intake of methyl-donor nutrients and child cognition at 3 years of age. Paediatric & Perinatal Epidemiology. 2012. 26:328-335. doi:10.1111/j.1365-3016.2012.01264.x.	Outcome
296.	Visentin, CE, Masih, SP, Plumptre, L, Schroder, TH, Kyoung-Jin, S, Ly, A, Lausman, AY, Berger, H, Croxford, R, Lamers, Y, Young-In, K, O'Connor, DL, Sohn, K-J, Kim, Young-In. Low Serum Vitamin B-12 Concentrations Are Prevalent in a Cohort of Pregnant Canadian Women. Journal of Nutrition. 2016. 146:1035-1042. doi:10.3945/jn.115.226845.	Intervention/Exposure
297.	Vitamin supplements. Medical Letter on Drugs and Therapeutics. 1985. 27:66-68.	Study Design; Outcome; Not primary data
298.	Viteri, FE, Casanueva, E, Tolentino, MC, Diaz-Frances, J, Erazo, AB. Antenatal iron supplements consumed daily produce oxidative stress in contrast to weekly supplementation in Mexican non-anemic women. Reprod Toxicol. 2012. 34:125-32. doi:10.1016/j.reprotox.2012.03.010.	Comparator
299.	Vujkovic, M, Steegers, EA, van Meurs, J, Yazdanpanah, N, van Rooij, IA, Uitterlinden, AG, Steegers-Theunissen, RP. The maternal homocysteine pathway is influenced by riboflavin intake and MTHFR polymorphisms without affecting the risk of orofacial clefts in the offspring. European Journal of Clinical Nutrition. 2010. 64:266-273. doi:10.1038/ejcn.2009.138.	Study Design; Intervention/Exposure
300.	Waksmańska, W, Bobiński, R, Ulman-Włodarz, I, Pielesz, A, Mikulska, M. The dietary composition of women who delivered preterm and full-term infants. Applied Nursing Research. 2017. 35:13-17. doi:10.1016/j.apnr.2017.02.013.	Outcome
301.	Wald, NJ, Hackshaw, A, Stone, R, Densem, J. Serum alpha-fetoprotein and neural tube defects in the first trimester of pregnancy. MRC Vitamin Study Research Group. Prenat Diagn. 1993. 13:1047-50.	Outcome
302.	Wald, NJ, Hackshaw, AK, Stone, R, Sourial, NA. Blood folic acid and vitamin B12 in relation to neural tube defects. British Journal of Obstetrics and Gynaecology. 1996. 103:319-324.	Intervention/Exposure
303.	Walker, MC, Finkelstein, SA, Rennicks White, R, Shachkina, S, Smith, GN, Wen, SW, Rodger, M. The Ottawa and Kingston (OaK) Birth Cohort: development and achievements. J Obstet Gynaecol Can. 2011. 33:1124-33.	Outcome

	Citation	Rationale
304.	Wallace, JM, Bonham, MP, Strain, J, Duffy, EM, Robson, PJ, Ward, M, McNulty, H, Davidson, PW, Myers, GJ, Shamlaye, CF, Clarkson, TW, Molloy, AM, Scott, JM, Ueland, PM. Homocysteine concentration, related B vitamins, and betaine in pregnant women recruited to the Seychelles Child Development Study. American Journal of Clinical Nutrition. 2008. 87:391-397.	Study Design; Intervention/Exposure; Outcome
305.	Wang, H, De Steur, H, Chen, G, Zhang, X, Pei, L, Gellynck, X, Zheng, X. Effectiveness of folic acid fortified flour for prevention of neural tube defects in a high risk region. Nutrients. 2016. 8. doi:10.3390/nu8030152.	Country
306.	Wang, Y, Zhao, N, Qiu, J, He, X, Zhou, M, Cui, H, Lv, L, Lin, X, Zhang, C, Zhang, H, Xu, R, Zhu, D, Dang, Y, Han, X, Bai, H, Chen, Y, Tang, Z, Lin, R, Yao, T, Su, J. Folic acid supplementation and dietary folate intake, and risk of preeclampsia. European Journal of Clinical Nutrition. 2015. 69:1145-1150. doi:10.1038/ejcn.2014.295.	Outcome
307.	Watanabe, H, Fukuoka, H, Sugiyama, T, Nagai, Y, Ogasawara, K, Yoshiike, N. Dietary folate intake during pregnancy and birth weight in Japan. European Journal of Nutrition. 2008. 47:341-347.	Intervention/Exposure
308.	Watermeyer, SR, Mukherjee, S, Myers, K, Parveen, S, Asaad, K. Severe megaloblastic anaemia compounding pre-eclampsia in a term pregnancy. J Obstet Gynaecol. 2004. 24:928-9. doi:10.1080/01443610400019096.	Study Design
309.	Wen, SW, Guo, Y, Rodger, M, White, RR, Yang, Q, Smith, GN, Perkins, SL, Walker, MC. Folic Acid Supplementation in Pregnancy and the Risk of Pre-Eclampsia-A Cohort Study. PLoS One. 2016. 11:e0149818. doi:10.1371/journal.pone.0149818.	Study Design
310.	Wen, SW, White, RR, Rybak, N, Gaudet, LM, Robson, S, Hague, W, Simms-Stewart, D, Carroli, G, Smith, G, Fraser, WD, Wells, G, Davidge, ST, Kingdom, J, Coyle, D, Fergusson, D, Corsi, DJ, Champagne, J, Sabri, E, Ramsay, T, Mol, BWJ, Oudijk, MA, Walker, MC. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. Bmj. 2018. 362:k3478. doi:10.1136/bmj.k3478.	Outcome
311.	West, AA, Yan, J, Perry, CA, Jiang, X, Malysheva, OV, Caudill, MA. Folate-status response to a controlled folate intake in nonpregnant, pregnant, and lactating women. Am J Clin Nutr. 2012. 96:789-800. doi:10.3945/ajcn.112.037523.	Comparator
312.	Yang, T, Gu, Y, Wei, X, Liang, X, Chen, J, Liu, Y, Zhang, T, Li, T. Periconceptional folic acid supplementation and vitamin B12 status in a cohort of Chinese early pregnancy women with the risk of adverse pregnancy outcomes. J Clin Biochem Nutr. 2017. 60:136-142. doi:10.3164/jcbn.16-45.	Study Design
313.	Yaremco, E, Inglis, A, Innis, SM, Hippman, C, Carrion, P, Lamers, Y, Honer, WG, Austin, J. Red blood cell folate levels in pregnant women with a history of mood disorders: a case series. Birth Defects Res A Clin Mol Teratol. 2013. 97:416-20. doi:10.1002/bdra.23144.	Study Design
314.	Yates, JR, Ferguson-Smith, MA, Shenkin, A, Guzman-Rodriguez, R, White, M, Clark, BJ. Is disordered folate metabolism the basis for the genetic predisposition to neural tube defects? Clin Genet. 1987. 31:279-87.	Intervention/Exposure

	Citation	Rationale
315.	Yila, TA, Araki, A, Sasaki, S, Miyashita, C, Itoh, K, Ikeno, T, Yoshioka, E, Kobayashi, S, Goudarzi, H, Baba, T, Braimoh, T, Minakami, H, Endo, T, Sengoku, K, Kishi, R. Predictors of folate status among pregnant Japanese women: the Hokkaido Study on Environment and Children's Health, 2002-2012. Br J Nutr. 2016. 115:2227-35. doi:10.1017/s0007114516001628.	Study Design
316.	Zhang, F, Yi, C, Fang, G, Sakutombo, DN. Dietary intakes and behaviours in pregnant women of Li ethnicity: a comparison of mountainous and coastal populations in southern China. Asia Pacific Journal of Clinical Nutrition. 2010. 19:236-242.	Study Design; Intervention/Exposure; Country
317.	Zhang, T, Xin, R, Gu, X, Wang, F, Pei, L, Lin, L, Chen, G, Wu, J, Zheng, X. Maternal serum vitamin B12, folate and homocysteine and the risk of neural tube defects in the offspring in a high-risk area of China. Public Health Nutrition. 2009. 12:680-686. doi:10.1017/S1368980008002735.	Intervention/Exposure; Country
318.	Zhu, X, Wei, L, Cao, D, Liu, C, Tian, J, Long, Y, Huang, S, Ou, L, Yang, X, Mo, Z. Low serum folate status in the second trimester increase the risk of low birthweight in Chinese women. Journal of Obstetrics & Gynaecology Research. 2018. 44:2037-2044. doi:10.1111/jog.13757.	Study Design
319.	Zhu, Z, Cheng, Y, Zeng, L, Elhoumed, M, He, G, Li, W, Zhang, M, Li, W, Li, D, Tsegaye, S, Chang, S, Yan, H, Wang, EY, Wang, D, Jaffar, S, Dibley, MJ. Association of Antenatal Micronutrient Supplementation With Adolescent Intellectual Development in Rural Western China: 14-Year Follow-up From a Randomized Clinical Trial. JAMA Pediatrics. 2018. 172:832-841. doi:10.1001/jamapediatrics.2018.1401.	Outcome; Country

Table 26. Articles excluded after full text screening with rationale for exclusion: Gestational diabetes and Hypertensive disorders of pregnancy

	Citation	Rationale
1.	A behavioural nutrition intervention for obese pregnant women: effects on diet quality, weight gain and the incidence of gestational diabetes. Australian and new zealand journal of obstetrics and gynaecology. 56 (4) (pp 364-373), 2016. Date of publication: 01 aug 2016.. 2016. #volume#:doi:10.1111/ajo.12474.	Intervention/Exposure
2.	Banhidy, F, Dakhlaoui, A, Dudas, I, Czeizel, AE. Birth outcomes of newborns after folic Acid supplementation in pregnant women with early and late pre-eclampsia: a population-based study. Adv Prev Med. 2011. 2011:127369. doi:10.4061/2011/127369.	Study Design; Outcome
3.	Barzilay, E, Moon, A, Plumptre, L, Masih, SP, Sohn, KJ, Visentin, CE, Ly, A, Malysheva, O, Croxford, R, Caudill, MA, O'Connor, DL, Kim, YI, Berger, H. Fetal one-carbon nutrient concentrations may be affected by gestational diabetes. Nutr Res. 2018. 55:57-64. doi:10.1016/j.nutres.2018.04.010.	Intervention/Exposure
4.	Bentley, S, Hermes, A, Phillips, D, Daoud, YA, Hanna, S. Comparative effectiveness of a prenatal medical food to prenatal vitamins on hemoglobin levels and adverse outcomes: a retrospective analysis. Clin Ther. 2011. 33:204-10. doi:10.1016/j.clinthera.2011.02.010.	Comparator

	Citation	Rationale
5.	Bergen, NE, Jaddoe, VW, Timmermans, S, Hofman, A, Lindemans, J, Russcher, H, Raat, H, Steegers-Theunissen, RP, Steegers, EA. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. Bjog. 2012. 119:739-51. doi:10.1111/j.1471-0528.2012.03321.x.	Intervention/Exposure; Outcome
6.	Berglund, SK, Garcia-Valdes, L, Torres-Espinola, FJ, Segura, MT, Martinez-Zaldivar, C, Aguilar, MJ, Agil, A, Lorente, JA, Florido, J, Padilla, C, Altmae, S, Marcos, A, Lopez-Sabater, MC, Campoy, C. Maternal, fetal and perinatal alterations associated with obesity, overweight and gestational diabetes: an observational cohort study (PREOBE). BMC Public Health. 2016. 16:207. doi:10.1186/s12889-016-2809-3.	Study Design; Comparator
7.	Bouthoorn, SH, Gaillard, R, Hofman, A, Jaddoe, V, Steegers, E, van Lenthe, F, Raat, H. OS036. Ethnic differences in blood pressure and hypertensivecomplications during pregnancy; the generation R Study. Pregnancy Hypertens. 2012. 2:195. doi:10.1016/j.preghy.2012.04.037.	Abstract
8.	Bouthoorn, SH, Gaillard, R, Hofman, A, Jaddoe, V, Steegers, E, van Lenthe, F, Raat, H. OS036. Ethnic differences in blood pressure and hypertensivecomplications during pregnancy; the generation R Study. Pregnancy Hypertens. 2012. 2:195. doi:10.1016/j.preghy.2012.04.037.	Abstract
9.	Bouthoorn, SH, Gaillard, R, Steegers, EA, Hofman, A, Jaddoe, VW, van Lenthe, FJ, Raat, H. Ethnic differences in blood pressure and hypertensive complications during pregnancy: the Generation R study. Hypertension. 2012. 60:198-205. doi:10.1161/hypertensionaha.112.194365.	Intervention/Exposure
10.	Braekke, K, Ueland, PM, Harsem, NK, Karlsen, A, Blomhoff, R, Staff, AC. Homocysteine, cysteine, and related metabolites in maternal and fetal plasma in preeclampsia. Pediatr Res. 2007. 62:319-24. doi:10.1203/PDR.0b013e318123fba2.	Intervention/Exposure
11.	Campbell, SK, Lynch, J, Esterman, A, McDermott, R. Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia. Matern Child Health J. 2012. 16:1284-92. doi:10.1007/s10995-011-0889-3.	Intervention/Exposure
12.	Chen, S, Li, N, Mei, Z, Ye, R, Li, Z, Liu, J, Serdula, MK. Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: A randomized clinical trial. Clin Nutr. 2019. 38:146-151. doi:10.1016/j.clnu.2018.01.029.	Country
13.	Cueto, HT, Riis, AH, Hatch, EE, Wise, LA, Rothman, KJ, Mikkelsen, EM. Predictors of preconceptional folic acid or multivitamin supplement use: a cross-sectional study of Danish pregnancy planners. Clin Epidemiol. 2012. 4:259-65. doi:10.2147/clep.S35463.	Study Design
14.	De Ocampo, MPG, Araneta, MRG, Macera, CA, Alcaraz, JE, Moore, TR, Chambers, CD. Folic acid supplement use and the risk of gestational hypertension and preeclampsia. Women Birth. 2018. 31:e77-e83. doi:10.1016/j.wombi.2017.08.128.	Intervention/Exposure; Comparator
15.	Dhobale, M, Chavan, P, Kulkarni, A, Mehendale, S, Pisal, H, Joshi, S. Reduced folate, increased vitamin B(12) and homocysteine concentrations in women delivering preterm. Ann Nutr Metab. 2012. 61:7-14. doi:10.1159/000338473 .	Intervention/Exposure; Comparator

	Citation	Rationale
16.	Ede, G, Keskin, U, Samur, G. Is there any effect of maternal dietary acid load during pregnancy on arising gestational diabetes mellitus? Journal of pediatric gastroenterology and nutrition. 2018. 66:932-.	Abstract
17.	Ede, G, Keskin, U, Samur, G. Is there any effect of maternal dietary acid load during pregnancy on arising gestational diabetes mellitus? Journal of pediatric gastroenterology and nutrition. 2018. 66:932-.	Abstract
18.	Egan, AM, Danyliv, A, Carmody, L, Kirwan, B, Dunne, FP. A Prepregnancy Care Program for Women With Diabetes: Effective and Cost Saving. J Clin Endocrinol Metab. 2016. 101:1807-15. doi:10.1210/jc.2015-4046.	Intervention/Exposure; Health Status
19.	Evers, IM, de Valk, HW, Visser, GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. Bmj. 2004. 328:915. doi:10.1136/bmj.38043.583160.EE.	Intervention/Exposure; Health Status
20.	Furness, D, Fenech, M, Dekker, G, Khong, TY, Roberts, C, Hague, W. Folate, vitamin B12, vitamin B6 and homocysteine: impact on pregnancy outcome. Matern Child Nutr. 2013. 9:155-66. doi:10.1111/j.1740-8709.2011.00364.x.	Intervention/Exposure; Outcome
21.	Furness, DL, Yasin, N, Dekker, GA, Thompson, SD, Roberts, CT. Maternal red blood cell folate concentration at 10-12 weeks gestation and pregnancy outcome. J Matern Fetal Neonatal Med. 2012. 25:1423-7. doi:10.3109/14767058.2011.636463.	Intervention/Exposure
22.	Garratt, FN. Pre-eclampsia: a challenge to public health teams worldwide to ensure that maternal diets contain adequate levels of folic acid, n3 polyunsaturated fatty acids and vitamin D at conception. Public Health. 2009. 123:95-6. doi:10.1016/j.puhe.2008.10.004.	Study Design
23.	Giroux, I, Inglis, SD, Lander, S, Gerrie, S, Mottola, MF. Dietary intake, weight gain, and birth outcomes of physically active pregnant women: a pilot study. Appl Physiol Nutr Metab. 2006. 31:483-9. doi:10.1139/h06-024 .	Intervention/Exposure
24.	Gray-Donald, K, Robinson, E, Collier, A, David, K, Renaud, L, Rodrigues, S. Intervening to reduce weight gain in pregnancy and gestational diabetes mellitus in Cree communities: an evaluation. Cmaj. 2000. 163:1247-51.	Intervention/Exposure
25.	Heifetz, EM, Birk, RZ. MTHFR C677T polymorphism affects normotensive diastolic blood pressure independently of blood lipids. Am J Hypertens. 2015. 28:387-92. doi:10.1093/ajh/hpu152.	Intervention/Exposure; Comparator
26.	Hernandez-Diaz, S, Werler, MM, Louik, C, Mitchell, AA. Risk of gestational hypertension in relation to folic acid supplementation during pregnancy. Am J Epidemiol. 2002. 156:806-12. doi:10.1093/aje/kwf129.	Study Design; Intervention/Exposure
27.	Hernandez-Diaz, S, Wu, XF, Hayes, C, Werler, MM, Ashok, TD, Badovinac, R, Kelsey, KT, Mitchell, AA. Methylenetetrahydrofolate reductase polymorphisms and the risk of gestational hypertension. Epidemiology. 2005. 16:628-34.	Study Design; Intervention/Exposure
28.	Huang, L, Yu, X, Li, L, Chen, Y, Yang, Y, Yang, Y, Hu, Y, Zhao, Y, Tang, H, Xu, D, Zhao, M. Duration of periconceptional folic acid supplementation and risk of gestational diabetes mellitus. Asia Pac J Clin Nutr. 2019. 28:321-329. doi:10.6133/apjcn.201906_28(2).0014 .	Intervention/Exposure; Comparator;

	Citation	Rationale
29.	Idzior-Walus, B, Cyganek, K, Sztefko, K, Seghieri, G, Breschi, MC, Walus-Miarka, M, Kawalec, E, Seretny, M, Sieradzki, J. Total plasma homocysteine correlates in women with gestational diabetes. Arch Gynecol Obstet. 2008. 278:309-13. doi:10.1007/s00404-008-0571-1 .	Intervention/Exposure; Comparator
30.	Johnson, AA, Knight, EM, Edwards, CH, Oyemade, UJ, Cole, OJ, Westney, OE, Westney, LS, Laryea, H, Jones, S. Dietary intakes, anthropometric measurements and pregnancy outcomes. J Nutr. 1994. 124:936s-942s. doi:10.1093/jn/124.suppl_6.936S.	Intervention/Exposure
31.	Kaplan, JS, Iqbal, S, England, BG, Zawacki, CM, Herman, WH. Is pregnancy in diabetic women associated with folate deficiency? Diabetes Care. 1999. 22:1017-21. doi:10.2337/diacare.22.7.1017.	Study Design; Intervention/Exposure
32.	Kharb, S, Aggarwal, D, Bala, J, Nanda, S. Evaluation of Homocysteine, Vitamin B12 and Folic Acid Levels During all the Trimesters in Pregnant and Preeclamptic Womens. Curr Hypertens Rev. 2016. 12:234-238. doi:10.2174/1573402112666161010151632 .	Intervention/Exposure
33.	Kim, MW, Ahn, KH, Ryu, KJ, Hong, SC, Lee, JS, Nava-Ocampo, AA, Oh, MJ, Kim, HJ. Preventive effects of folic acid supplementation on adverse maternal and fetal outcomes. PLoS One. 2014. 9:e97273. doi:10.1371/journal.pone.0097273.	Study Design
34.	Kim, MW, Hong, SC, Choi, JS, Han, JY, Oh, MJ, Kim, HJ, Nava-Ocampo, A, Koren, G. Homocysteine, folate and pregnancy outcomes. J Obstet Gynaecol. 2012. 32:520-4. doi:10.3109/01443615.2012.693984.	Study Design; Intervention/Exposure
35.	Leeda, M, Riyazi, N, de Vries, JI, Jakobs, C, van Geijn, HP, Dekker, GA. Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and a history of preeclampsia or fetal growth restriction. Am J Obstet Gynecol. 1998. 179:135-9. doi:10.1016/s0002-9378(98)70263-7.	Intervention/Exposure; Comparator; Population
36.	Li, M, Li, S, Chavarro, JE, Gaskins, AJ, Ley, SH, Hinkle, SN, Wang, X, Ding, M, Bell, G, Bjerregaard, AA, Olsen, SF, Mills, JL, Hu, FB, Zhang, C. Prepregnancy Habitual Intakes of Total, Supplemental, and Food Folate and Risk of Gestational Diabetes Mellitus: A Prospective Cohort Study. Diabetes Care. 2019. 42:1034-1041. doi:10.2337/dc18-2198.	Population; Exposure measured >6 mo before pregnancy
37.	Li, Z, Gueant-Rodriguez, RM, Quilliot, D, Sirveaux, MA, Meyre, D, Gueant, JL, Brunaud, L. Folate and vitamin B12 status is associated with insulin resistance and metabolic syndrome in morbid obesity. Clin Nutr. 2018. 37:1700-1706. doi:10.1016/j.clnu.2017.07.008.	Intervention/Exposure
38.	Li, Z, Ye, R, Zhang, L, Li, H, Liu, J, Ren, A. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension. 2013. 61:873-9. doi:10.1161/hypertensionaha.111.00230.	Country
39.	Looman, M, Geelen, A, Samlal, RAK, Heijligenberg, R, Klein Gunnewiek, JMT, Balvers, MGJ, Wijnberger, LDE, Brouwer-Brolsma, EM, Feskens, EJM. Changes in Micronutrient Intake and Status, Diet Quality and Glucose Tolerance from Preconception to the Second Trimester of Pregnancy. Nutrients. 2019. 11:doi:10.3390/nu11020460.	Intervention/Exposure

	Citation	Rationale
40.	Looman, M, Schoenaker, Dajm, Soedamah-Muthu, SS, Mishra, GD, Geelen, A, Feskens, EJM. Pre-pregnancy dietary micronutrient adequacy is associated with lower risk of developing gestational diabetes in Australian women. Nutr Res. 2019. 62:32-40. doi:10.1016/j.nutres.2018.11.006.	Intervention/Exposure
41.	Lopez-Alarcon, M, Montalvo-Velarde, I, Vital-Reyes, VS, Hinojosa-Cruz, JC, Leanos-Miranda, A, Martinez-Basila, A. Serial determinations of asymmetric dimethylarginine and homocysteine during pregnancy to predict pre-eclampsia: a longitudinal study. Bjog. 2015. 122:1586-92. doi:10.1111/1471-0528.13516.	Intervention/Exposure; Comparator
42.	Lucock, M, Yates, Z, Martin, C, Choi, JH, Boyd, L, Tang, S, Naumovski, N, Furst, J, Roach, P, Jablonski, N, Chaplin, G, Veysey, M. Vitamin D, folate, and potential early lifecycle environmental origin of significant adult phenotypes. Evol Med Public Health. 2014. 2014:69-91. doi:10.1093/emph/eou013.	Intervention/Exposure; Population
43.	Makedos, G, Papanicolaou, A, Hitoglou, A, Kalogiannidis, I, Makedos, A, Vrazioti, V, Goutzioulis, M. Homocysteine, folic acid and B12 serum levels in pregnancy complicated with preeclampsia. Arch Gynecol Obstet. 2007. 275:121-4. doi:10.1007/s00404-006-0223-2.	Intervention/Exposure
44.	Mardones, F, Urrutia, MT, Villarroel, L, Rioseco, A, Castillo, O, Rozowski, J, Tapia, JL, Bastias, G, Bacallao, J, Rojas, I. Effects of a dairy product fortified with multiple micronutrients and omega-3 fatty acids on birth weight and gestation duration in pregnant Chilean women. Public Health Nutrition. 2008. 11:30-40. doi:10.1017/S1368980007000110.	Intervention/Exposure; Comparator
45.	Martinussen, MP, Bracken, MB, Triche, EW, Jacobsen, GW, Risnes, KR. Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2015. 195:94-9. doi:10.1016/j.ejogrb.2015.09.022.	Intervention/Exposure
46.	Meinila, J, Koivusalo, SB, Valkama, A, Rono, K, Erkkola, M, Kautiainen, H, Stach-Lempinen, B, Eriksson, JG. Nutrient intake of pregnant women at high risk of gestational diabetes. Food Nutr Res. 2015. 59:26676. doi:10.3402/fnr.v59.26676.	Study Design; Intervention/Exposure
47.	Meltzer, HM, Brantsaeter, AL, Nilsen, RM, Magnus, P, Alexander, J, Haugen, M. Effect of dietary factors in pregnancy on risk of pregnancy complications: results from the Norwegian Mother and Child Cohort Study. Am J Clin Nutr. 2011. 94:1970s-1974s. doi:10.3945/ajcn.110.001248.	Study Design; Intervention/Exposure
48.	Mislanova, C, Martsenyuk, O, Huppertz, B, Obolenskaya, M. Placental markers of folate-related metabolism in preeclampsia. Reproduction. 2011. 142:467-76. doi:10.1530/rep-10-0484.	Intervention/Exposure
49.	Mogaddam, MR, Ardebili, NS, Kariman, N. The relation between the incidence rate of second and third trimester hemoglobin and the incidence of preeclampsia and gestational diabetes: A cohort study. Crescent Journal of Medical and Biological Sciences. 2019. 6:85-90.	Intervention/Exposure
50.	Oken, E, Ning, Y, Rifas-Shiman, SL, Rich-Edwards, JW, Olsen, SF, Gillman, MW. Diet during pregnancy and risk of preeclampsia or gestational hypertension. Ann Epidemiol. 2007. 17:663-8. doi:10.1016/j.annepidem.2007.03.003.	Intervention/Exposure

	Citation	Rationale
51.	Patrick, TE, Powers, RW, Daftary, AR, Ness, RB, Roberts, JM. Homocysteine and folic acid are inversely related in black women with preeclampsia. Hypertension. 2004. 43:1279-82. doi:10.1161/01.HYP.0000126580.81230.da.	Intervention/Exposure
52.	Powers, RW, Dunbar, MS, Gallaher, MJ, Roberts, JM. The 677 C-T methylenetetrahydrofolate reductase mutation does not predict increased maternal homocysteine during pregnancy. Obstet Gynecol. 2003. 101:762-6.	Intervention/Exposure
53.	Ray, JG, Mamdani, MM. Association between folic acid food fortification and hypertension or preeclampsia in pregnancy. Arch Intern Med. 2002. 162:1776-7.	Study Design
54.	Roland, JM, Murphy, HR, Ball, V, Northcote-Wright, J, Temple, RC. The pregnancies of women with Type 2 diabetes: poor outcomes but opportunities for improvement. Diabet Med. 2005. 22:1774-7. doi:10.1111/j.1464-5491.2005.01784.x.	Health Status
55.	Salmenhaara, M, Uusitalo, L, Uusitalo, U, Kronberg-Kippila, C, Sinkko, H, Ahonen, S, Veijola, R, Knip, M, Kaila, M, Virtanen, SM. Diet and weight gain characteristics of pregnant women with gestational diabetes. Eur J Clin Nutr. 2010. 64:1433-40. doi:10.1038/ejcn.2010.167.	Study Design
56.	Sanchez, SE, Zhang, C, Rene Malinow, M, Ware-Jauregui, S, Larrabure, G, Williams, MA. Plasma folate, vitamin B(12), and homocyst(e)ine concentrations in preeclamptic and normotensive Peruvian women. Am J Epidemiol. 2001. 153:474-80. doi:10.1093/aje/153.5.474.	Intervention/Exposure; Country
57.	Sanlikan, F, Tufan, F, Gocmen, A, Kabadayi, C, Sengul, E. The evaluation of homocysteine level in patients with preeclampsia. Ginekol Pol. 2015. 86:287-91.	Intervention/Exposure
58.	Shen, M, Smith, GN, Rodger, M, White, RR, Walker, MC, Wen, SW. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS One. 2017. 12:e0175914. doi:10.1371/journal.pone.0175914.	Duplicate
59.	Stone, LP, Stone, PM, Rydbom, EA, Stone, LA, Stone, TE, Wilkens, LE, Reynolds, K. Customized nutritional enhancement for pregnant women appears to lower incidence of certain common maternal and neonatal complications: an observational study. Glob Adv Health Med. 2014. 3:50-5. doi:10.7453/gahmj.2014.053.	Intervention/Exposure; Comparator
60.	Sun, F, Qian, W, Zhang, C, Fan, JX, Huang, HF. Correlation of Maternal Serum Homocysteine in the First Trimester with the Development of Gestational Hypertension and Preeclampsia. Med Sci Monit. 2017. 23:5396-5401. doi:10.12659/msm.905055.	Intervention/Exposure
61.	Suzuki, Y, Yamamoto, T, Matsuura, A. PP049. Could the supplementation of L-arginine plus folic acid T improve reduced endothelial function seen in preeclampsia? Pregnancy Hypertens. 2012. 2:268. doi:10.1016/j.preghy.2012.04.160.	Abstract
62.	Suzuki, Y, Yamamoto, T, Matsuura, A. PP049. Could the supplementation of L-arginine plus folic acid T improve reduced endothelial function seen in preeclampsia? Pregnancy Hypertens. 2012. 2:268. doi:10.1016/j.preghy.2012.04.160.	Abstract

	Citation	Rationale
63.	Theriault, S, Giguere, Y, Masse, J, Lavoie, SB, Girouard, J, Bujold, E, Forest, JC. Absence of association between serum folate and preeclampsia in women exposed to food fortification. Obstet Gynecol. 2013. 122:345-51. doi:10.1097/AOG.0b013e31829b2f7c.	Intervention/Exposure
64.	Thompson, D, Berger, H, Feig, D, Gagnon, R, Kader, T, Keely, E, Kozak, S, Ryan, E, Sermer, M, Vinokuroff, C. Diabetes and Pregnancy. Canadian Journal of Diabetes. 2013. 37:S168-S183. doi:10.1016/j.jcjd.2013.01.044.	Study Design
65.	Timmermans, S, Jaddoe, VW, Silva, LM, Hofman, A, Raat, H, Steegers-Theunissen, RP, Steegers, EA. Folic acid is positively associated with uteroplacental vascular resistance: the Generation R study. Nutr Metab Cardiovasc Dis. 2011. 21:54-61. doi:10.1016/j.numecd.2009.07.002.	Intervention/Exposure
66.	Wang, Y, Zhao, N, Qiu, J, He, X, Zhou, M, Cui, H, Lv, L, Lin, X, Zhang, C, Zhang, H, Xu, R, Zhu, D, Dang, Y, Han, X, Zhang, H, Bai, H, Chen, Y, Tang, Z, Lin, R, Yao, T, Su, J, Xu, X, Liu, X, Wang, W, Ma, B, Liu, S, Qiu, W, Huang, H, Liang, J, Wang, S, Ehrenkranz, RA, Kim, C, Liu, Q, Zhang, Y. Folic acid supplementation and dietary folate intake, and risk of preeclampsia. Eur J Clin Nutr. 2015. 69:1145-1150. doi:10.1038/ejcn.2014.295.	Intervention/Exposure; Comparator
67.	Watermeyer, SR, Mukherjee, S, Myers, K, Parveen, S, Asaad, K. Severe megaloblastic anaemia compounding pre-eclampsia in a term pregnancy. J Obstet Gynaecol. 2004. 24:928-9. doi:10.1080/01443610400019096.	Study Design
68.	Wen, SW, Chen, XK, Rodger, M, White, RR, Yang, Q, Smith, GN, Sigal, RJ, Perkins, SL, Walker, MC. Folic acid supplementation in early second trimester and the risk of preeclampsia. Am J Obstet Gynecol. 2008. 198:45.e1-7. doi:10.1016/j.ajog.2007.06.067.	Duplicate
69.	Wen, SW, White, RR, Rybak, N, Gaudet, LM, Robson, S, Hague, W, Simms-Stewart, D, Carroli, G, Smith, G, Fraser, WD, Wells, G, Davidge, ST, Kingdom, J, Coyle, D, Fergusson, D, Corsi, DJ, Champagne, J, Sabri, E, Ramsay, T, Mol, BWJ, Oudijk, MA, Walker, MC. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. Bmj. 2018. 362:k3478. doi:10.1136/bmj.k3478.	Intervention/Exposure; Comparator
70.	Williams, MA, Sanchez, SE, Zhang, C, Bazul, V. Methylenetetrahydrofolate reductase 677 C-->T polymorphism and plasma folate in relation to pre-eclampsia risk among Peruvian women. J Matern Fetal Neonatal Med. 2004. 15:337-44. doi:10.1080/14767050410001680037.	Intervention/Exposure; Country
71.	Yajnik, CS, Deshpande, SS, Jackson, AA, Refsum, H, Rao, S, Fisher, DJ, Bhat, DS, Naik, SS, Coyaji, KJ, Joglekar, CV, Joshi, N, Lubree, HG, Deshpande, VU, Rege, SS, Fall, CH. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 2008. 51:29-38. doi:10.1007/s00125-007-0793-y.	Country; Outcome

Table 27. Articles excluded after full text screening with rationale for exclusion: Developmental milestones, including neurocognitive development

	Citation	Rationale
1.	Ars, CL, Nijs, IM, Marroun, HE, Muetzel, R, Schmidt, M, Steenweg-de Graaff, J, van der Lugt, A, Jaddoe, VW, Hofman, A, Steegers, EA, Verhulst, FC, Tiemeier, H, White, T. Prenatal folate, homocysteine and vitamin B12 levels and child brain volumes, cognitive development and psychological functioning: the Generation R Study. Br J Nutr. 2016. 1-9. doi:10.1017/s0007114515002081.	Intervention/Exposure
2.	Bjork, M, Riedel, B, Spigset, O, Veiby, G, Kolstad, E, Daltveit, AK, Gilhus, NE. Association of Folic Acid Supplementation During Pregnancy With the Risk of Autistic Traits in Children Exposed to Antiepileptic Drugs In Utero. JAMA Neurol. 2018. 75:160-168. doi:10.1001/jamaneurol.2017.3897.	Comparator
3.	Braun, JM, Froehlich, T, Kalkbrenner, A, Pfeiffer, CM, Fazili, Z, Yolton, K, Lanphear, BP. Brief report: are autistic-behaviors in children related to prenatal vitamin use and maternal whole blood folate concentrations? J Autism Dev Disord. 2014. 44:2602-7. doi:10.1007/s10803-014-2114-x.	Intervention/Exposure; Comparator
4.	Brown, AS, Susser, ES. Prenatal nutritional deficiency and risk of adult schizophrenia. Schizophr Bull. 2008. 34:1054-63. doi:10.1093/schbul/sbn096.	Study Design; Review
5.	Chatzi, L, Papadopoulou, E, Koutra, K, Roumeliotaki, T, Georgiou, V, Stratakis, N, Lebentakou, V, Karachaliou, M, Vassilaki, M, Kogevinas, M. Effect of high doses of folic acid supplementation in early pregnancy on child neurodevelopment at 18 months of age: the mother-child cohort 'Rhea' study in Crete, Greece. Public Health Nutr. 2012. 15:1728-36. doi:10.1017/s1368980012000067.	Intervention/Exposure; Comparator
6.	del Rio Garcia, C, Torres-Sanchez, L, Chen, J, Schnaas, L, Hernandez, C, Osorio, E, Portillo, MG, Lopez-Carrillo, L. Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment. Nutr Neurosci. 2009. 12:13-20. doi:10.1179/147683009x388913.	Intervention/Exposure
7.	DeVilbiss, EA, Magnusson, C, Gardner, RM, Rai, D, Newschaffer, CJ, Lyall, K, Dalman, C, Lee, BK. Antenatal nutritional supplementation and autism spectrum disorders in the Stockholm youth cohort: population based cohort study. Bmj. 2017. 359:j4273. doi:10.1136/bmj.j4273.	Intervention/Exposure; Comparator
8.	Dobo, M, Czeizel, AE. Long-term somatic and mental development of children after periconceptional multivitamin supplementation. Eur J Pediatr. 1998. 157:719-23.	Comparator
9.	D'Souza, S, Waldie, KE, Peterson, ER, Underwood, L, Morton, SMB. Antenatal and Postnatal Determinants of Behavioural Difficulties in Early Childhood: Evidence from Growing Up in New Zealand. Child Psychiatry Hum Dev. 2019. 50:45-60. doi:10.1007/s10578-018-0816-6.	Comparator
10.	Eryilmaz, H, Dowling, KF, Huntington, FC, Rodriguez-Thompson, A, Soare, TW, Beard, LM, Lee, H, Blossom, JC, Gollub, RL, Susser, E, Gur, RC, Calkins, ME, Gur, RE, Satterthwaite, TD, Roffman, JL. Association of Prenatal Exposure to Population-Wide Folic Acid Fortification With Altered Cerebral Cortex Maturation in Youths. JAMA Psychiatry. 2018. 75:918-928. doi:10.1001/jamapsychiatry.2018.1381.	Intervention/Exposure; Population

	Citation	Rationale
11.	Forns, J, Torrent, M, Garcia-Esteban, R, Caceres, A, Pilar Gomila, M, Martinez, D, Morales, E, Julvez, J, Grimalt, JO, Sunyer, J. Longitudinal association between early life socio-environmental factors and attention function at the age 11 years. Environ Res. 2012. 117:54-9. doi:10.1016/j.envres.2012.04.007.	Intervention/Exposure; Comparator
12.	Frye, RE, Slattery, JC, Quadros, EV. Folate metabolism abnormalities in autism: potential biomarkers. Biomark Med. 2017. 11:687-699. doi:10.2217/bmm-2017-0109.	Study Design; Review
13.	Gatica-Domínguez, G, Rothenberg, SJ, Torres-Sánchez, L, Schnaas, L, Stein, AD, Schmidt, RJ, López-Carrillo, L. The association of prenatal folate and vitamin B12 levels with postnatal neurodevelopment varies by maternal MTHFR 677C>T genotype. International Journal of Behavioral Development. 2019. doi:10.1177/0165025419853379.	Intervention/Exposure
14.	Georgieff, MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr. 2007. 85:614s-620s. doi:10.1093/ajcn/85.2.614S.	Study Design; Intervention/Exposure; Not primary research
15.	Glaser, B, Ades, AE, Lewis, S, Emmet, P, Lewis, G, Smith, GD, Zammit, S. Perinatal folate-related exposures and risk of psychotic symptoms in the ALSPAC birth cohort. Schizophr Res. 2010. 120:177-83. doi:10.1016/j.schres.2010.03.006.	Outcome
16.	Goodrich, AJ, Volk, HE, Tancredi, DJ, McConnell, R, Lurmann, FW, Hansen, RL, Schmidt, RJ. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res. 2018. 11:69-80. doi:10.1002/aur.1885.	Study Design
17.	Husebye, ESN, Gilhus, NE, Riedel, B, Spigset, O, Daltveit, AK, Bjork, MH. Verbal abilities in children of mothers with epilepsy: Association to maternal folate status. Neurology. 2018. 91:e811-e821. doi:10.1212/wnl.0000000000006073.	Comparator
18.	Irwin, R, Caffrey, A, McLaughlin, M, McNulty, H, Cassidy, T, Pentieva, K, Walsh, C. Beneficial effects on psychosocial and cognitive development observed in children following in utero folic acid supplementation track with changes in their DNA methylation. Ulster medical journal. 2018. 87:56-.	Abstract
19.	Julvez, J, Fortuny, J, Mendez, M, Torrent, M, Ribas-Fito, N, Sunyer, J. Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. Paediatr Perinat Epidemiol. 2009. 23:199-206. doi:10.1111/j.1365-3016.2009.01032.x.	Intervention/Exposure; Comparator
20.	Katz, JM, Pacia, SV, Devinsky, O. Current Management of Epilepsy and Pregnancy: Fetal Outcome, Congenital Malformations, and Developmental Delay. Epilepsy Behav. 2001. 2:119-123. doi:10.1006/ebeh.2001.0158.	Health Status
21.	Lai, JS, Mohamad Ayob, MN, Cai, S, Quah, PL, Gluckman, PD, Shek, LP, Yap, F, Tan, KH, Chong, YS, Godfrey, KM, Meaney, MJ, Broekman, BFP, Rifkin-Graboi, A, Chong, MFF. Maternal plasma vitamin B12 concentrations during pregnancy and infant cognitive outcomes at 2 years of age. Br J Nutr. 2019. 1-26. doi:10.1017/s0007114519000746.	Intervention/Exposure

	Citation	Rationale
22.	Li, YM, Shen, YD, Li, YJ, Xun, GL, Liu, H, Wu, RR, Xia, K, Zhao, JP, Ou, JJ. Maternal dietary patterns, supplements intake and autism spectrum disorders: A preliminary case-control study. Medicine (Baltimore). 2018. 97:e13902. doi:10.1097/md.0000000000013902.	Study Design
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